Beth Israel Deaconess Medical Center

A major teaching hospital of Harvard Medical School

Challenges in Designing Cancer Vaccines as Effective Immunotherapy

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Dana Farber Harvard Cancer Center

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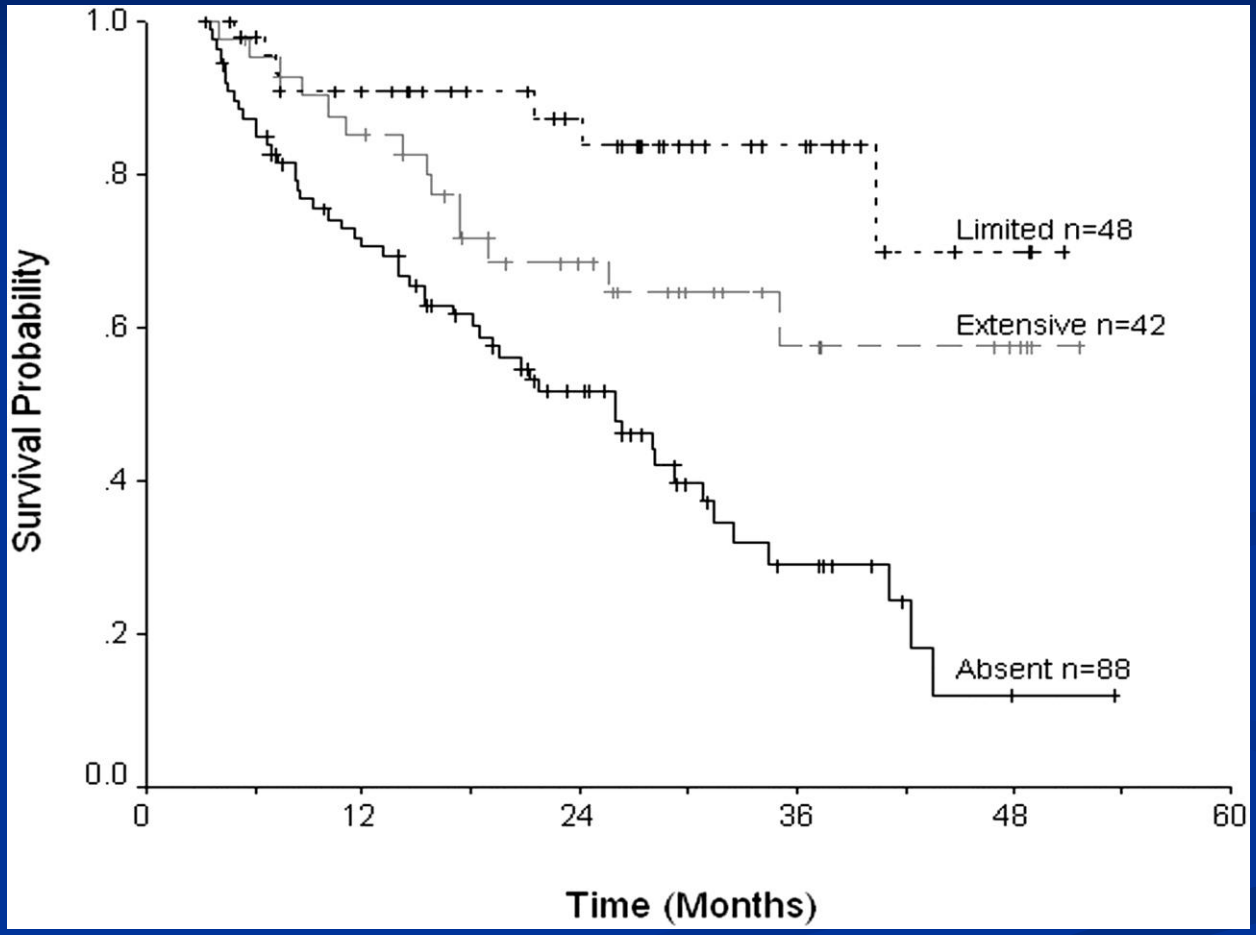
Efficacy of Cellular Immunotherapy for Myeloma: Graft versus Disease Effect



Crawley, C. et al. Blood 2005;105:4532-4539

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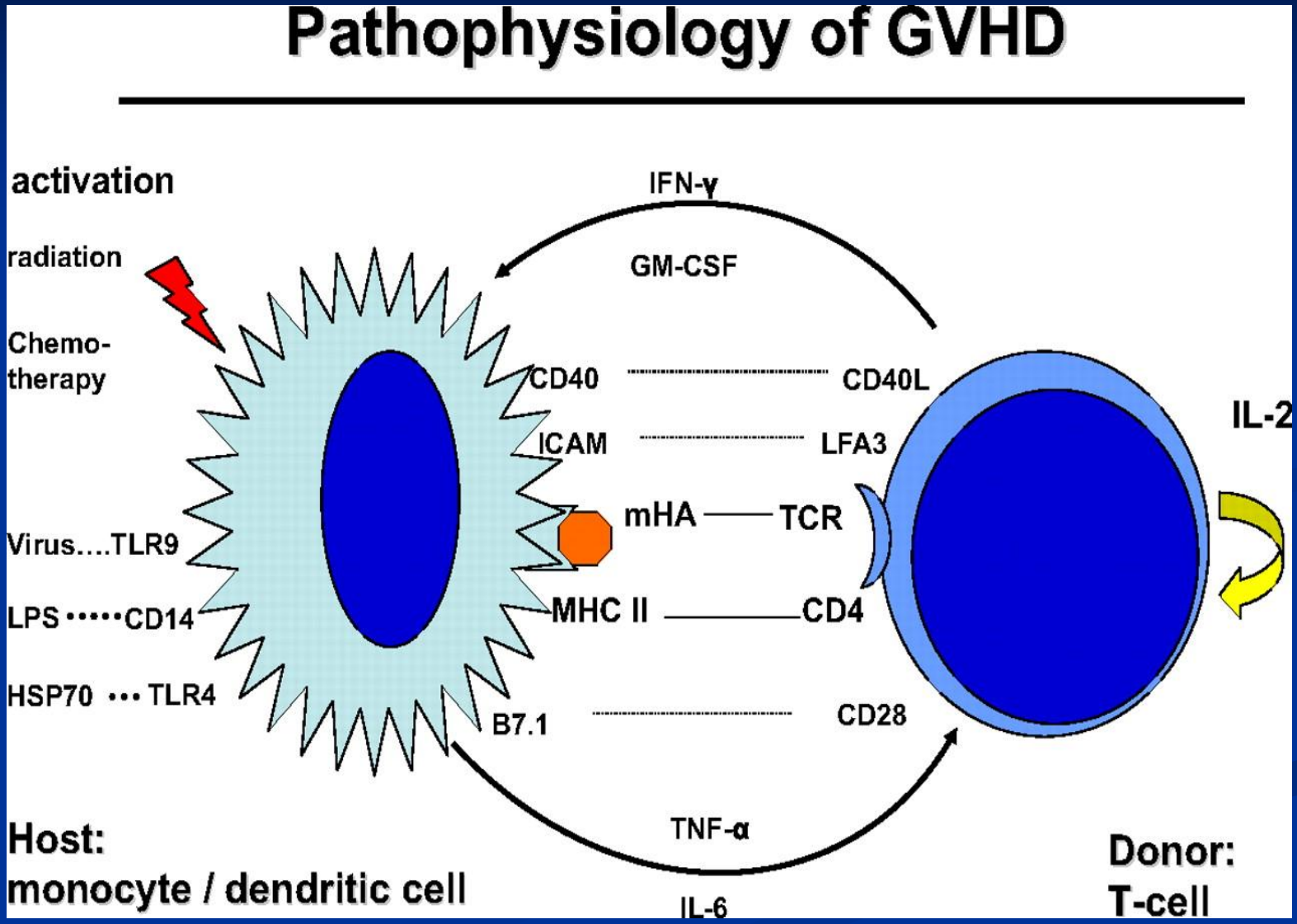
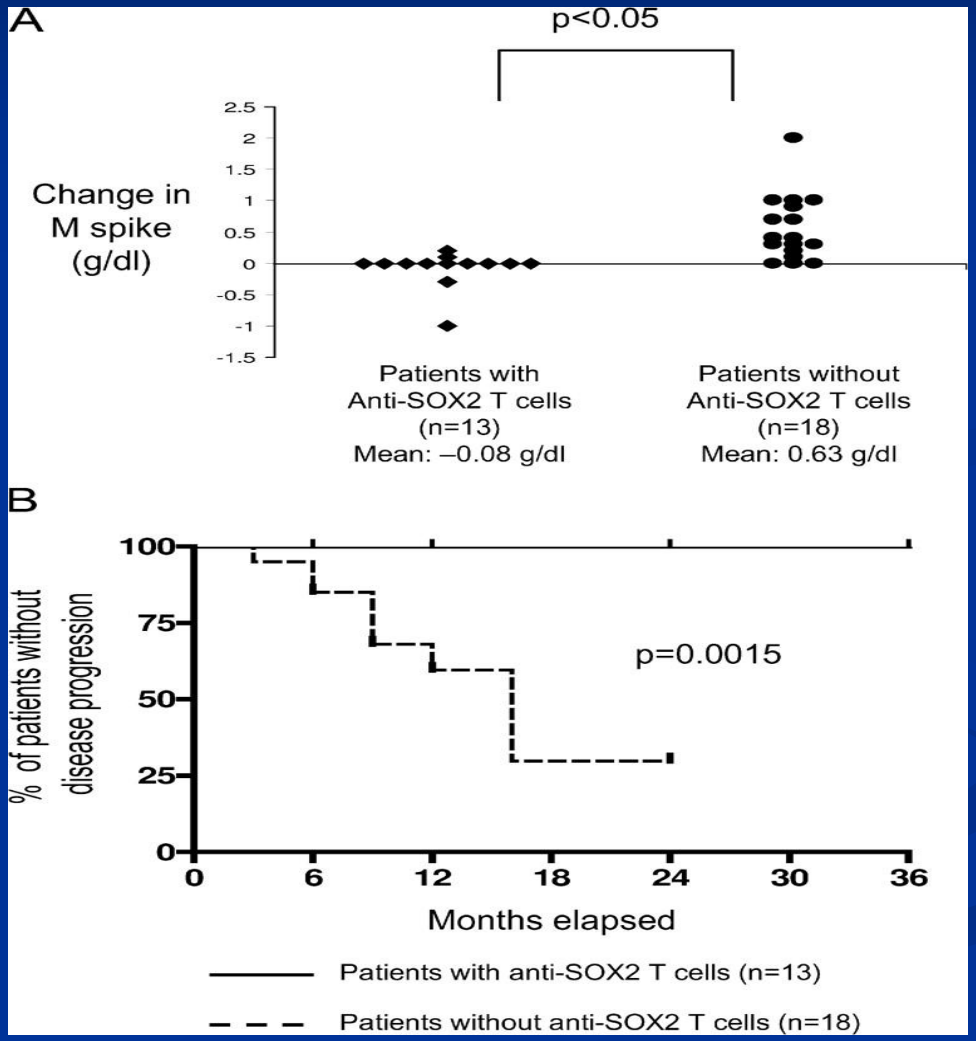


Kolb H Blood 2008;112:4371-4383

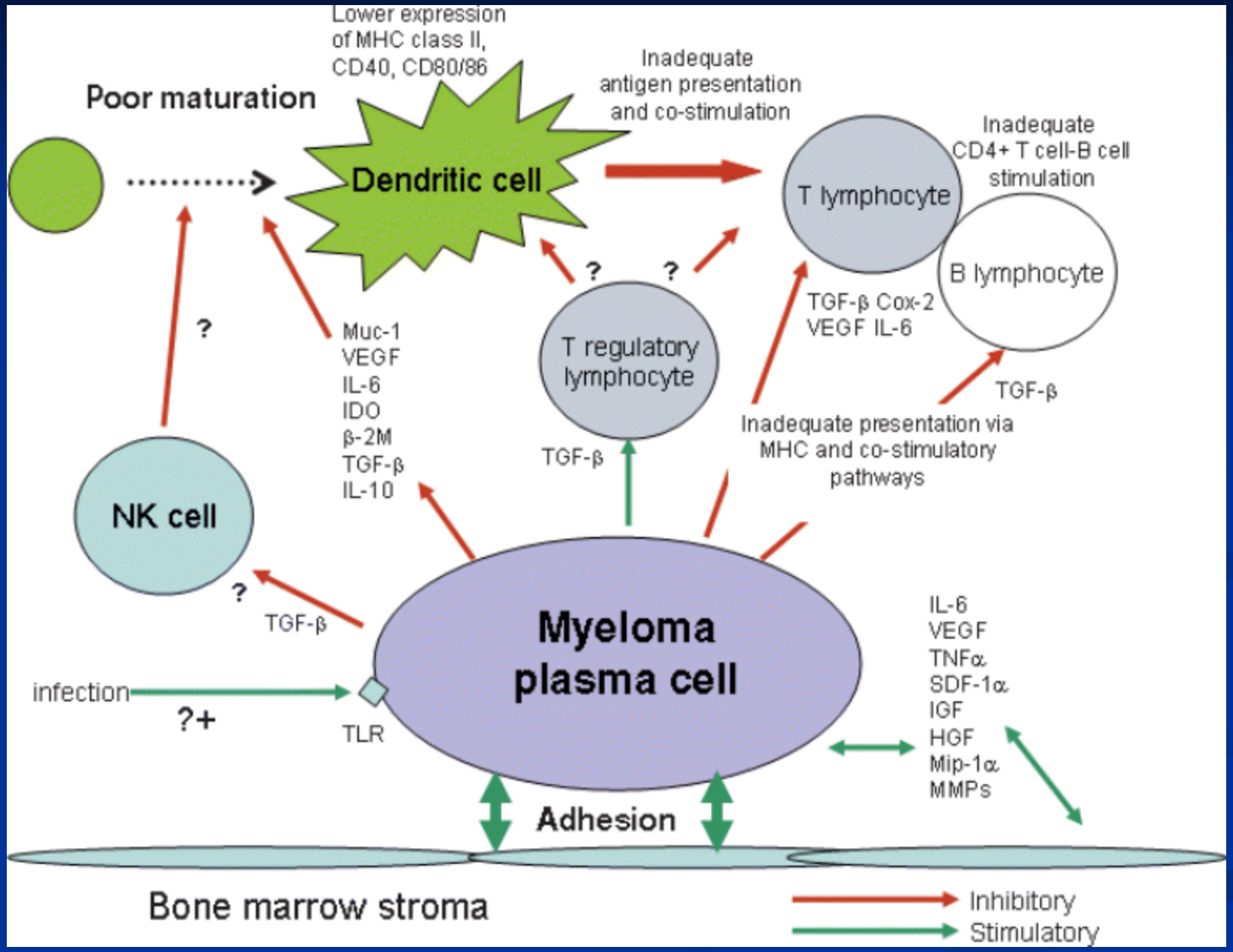
Cutaneous Acute GVHD

Can Tumor Vaccines Selectively Target Multiple Myeloma and Induce Clinically Meaningful Disease Response?

Correlation of detectable SOX2-reactive T cell immunity with clinical outcome in patients with asymptomatic plasmaproliferative disorders.



Spisek R et al. J Exp Med 2007;204:831-840

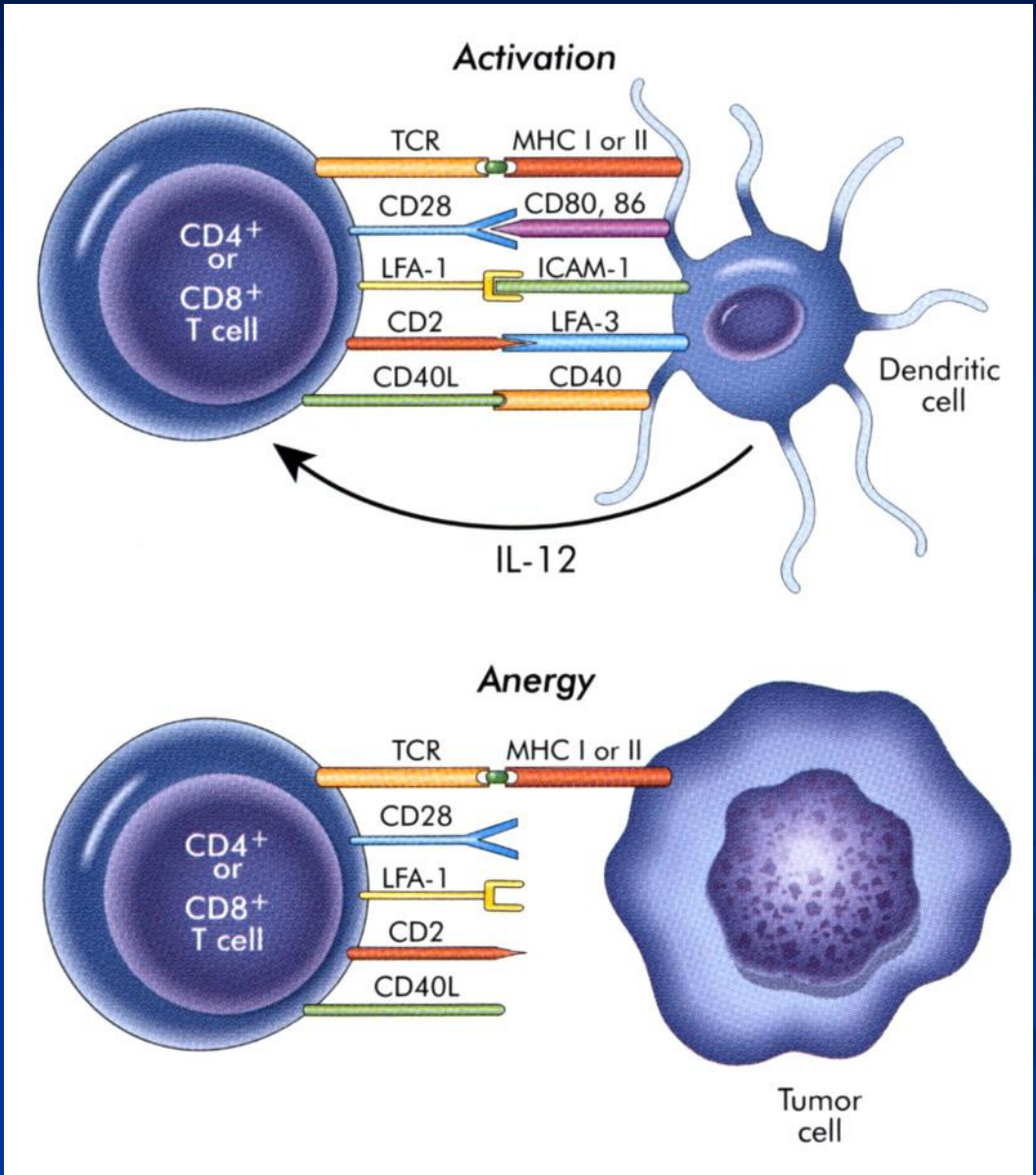


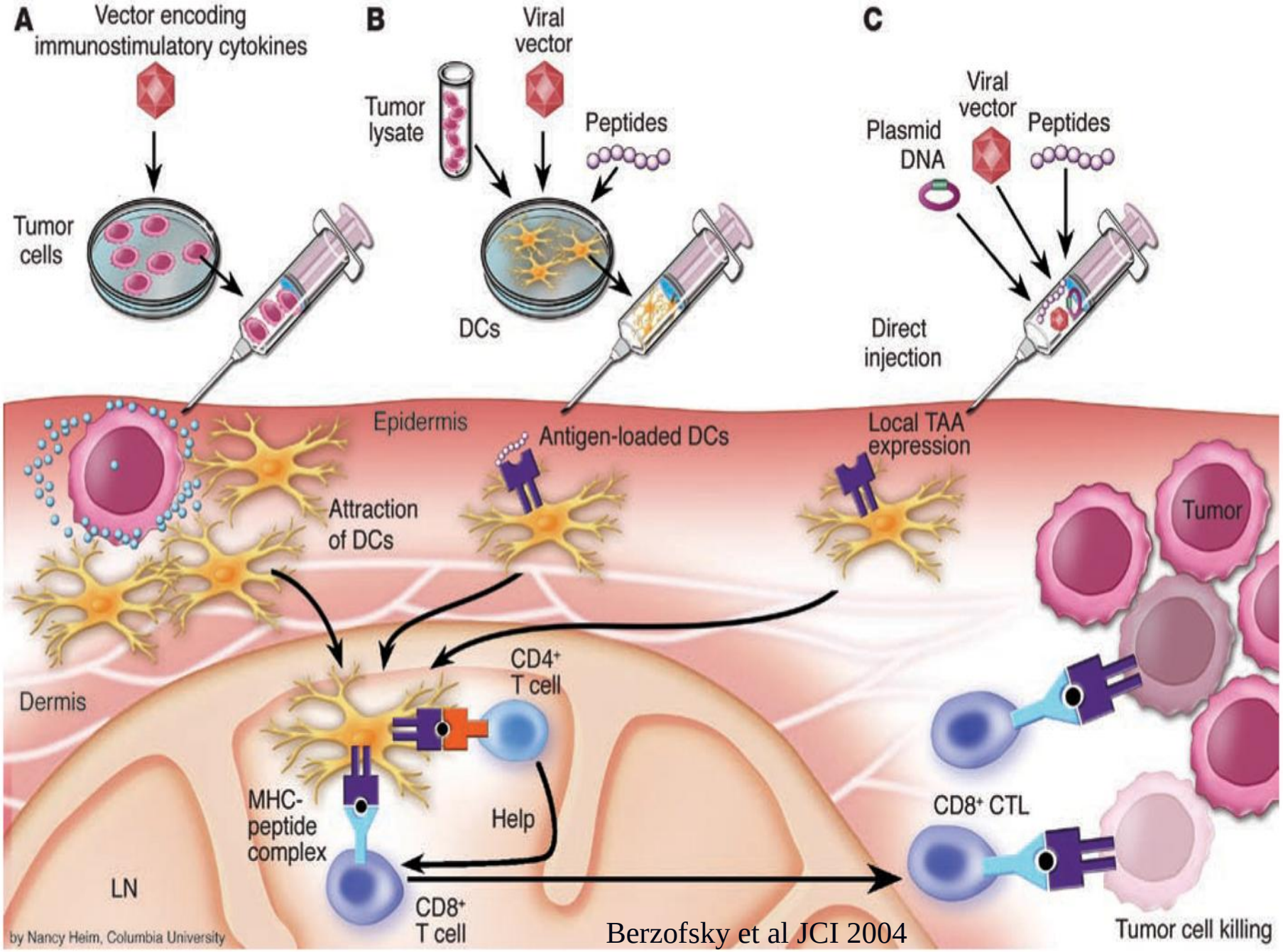
Guy Pratt, BJH, 2007

Designing an Effective Cancer Vaccine

- Enhancing antigen presentation
  - Defining optimal antigenic targets
  - Effective antigen presentation to result in activation rather than tolerance
- Reversing the immunosuppressive milieu
  - Reversing effector cell dysfunction
  - Reduction in inhibitory cells
- Breaking tolerance establishing durable anti-tumor immunity
  - Downregulation of inhibitory pathways
- Targeting tumor heterogeneity

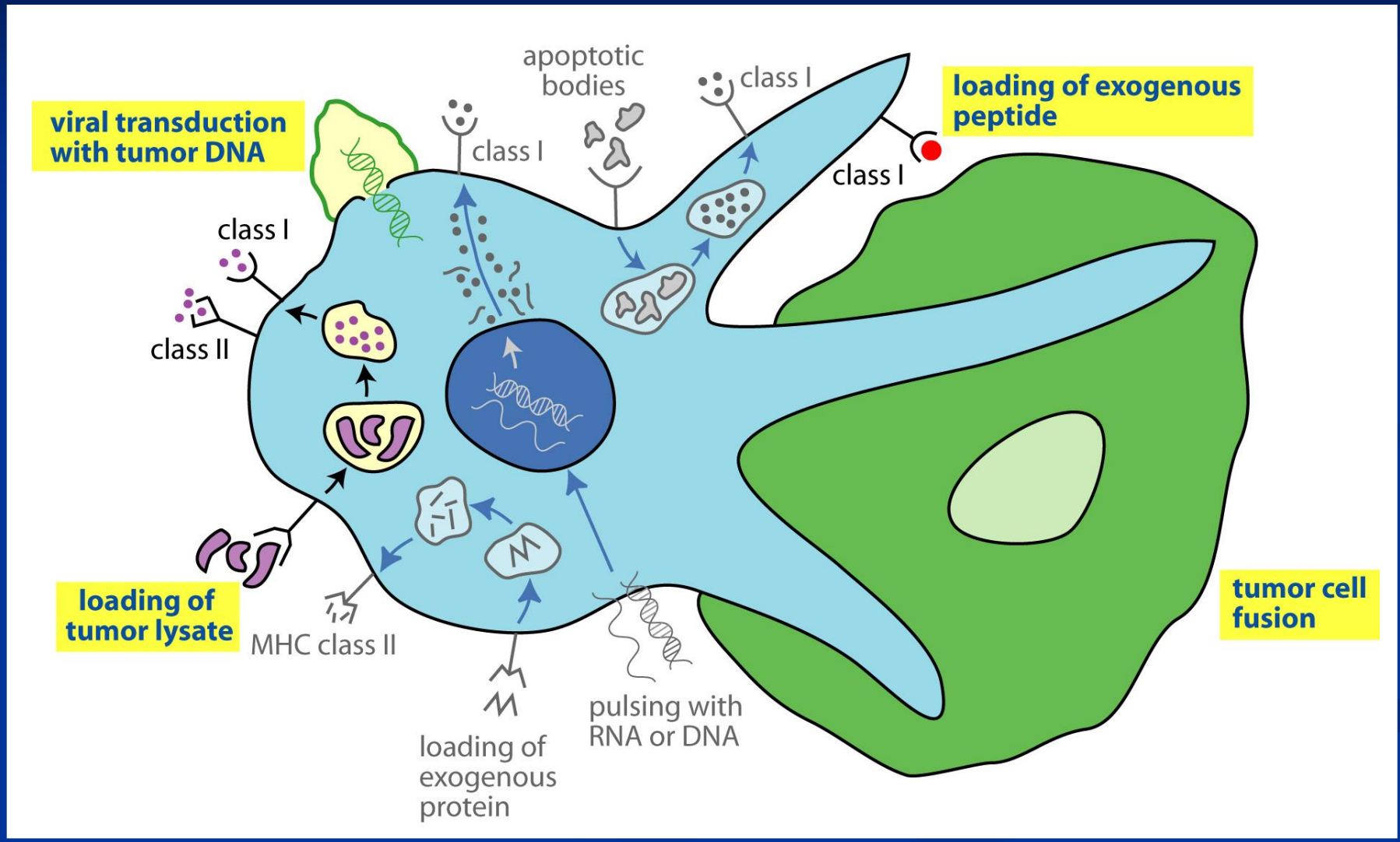
Antigen Presentation





Berzofsky et al JCI 2004

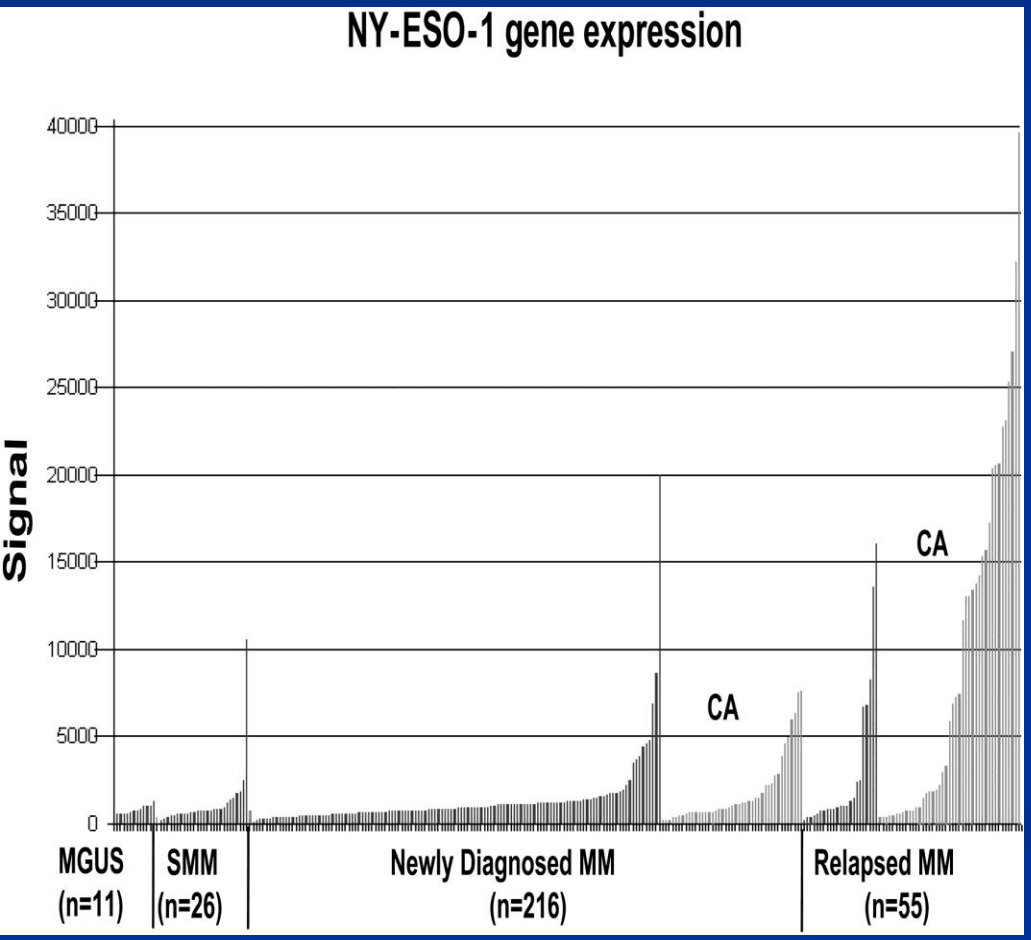
Strategies to load tumor antigens onto DC

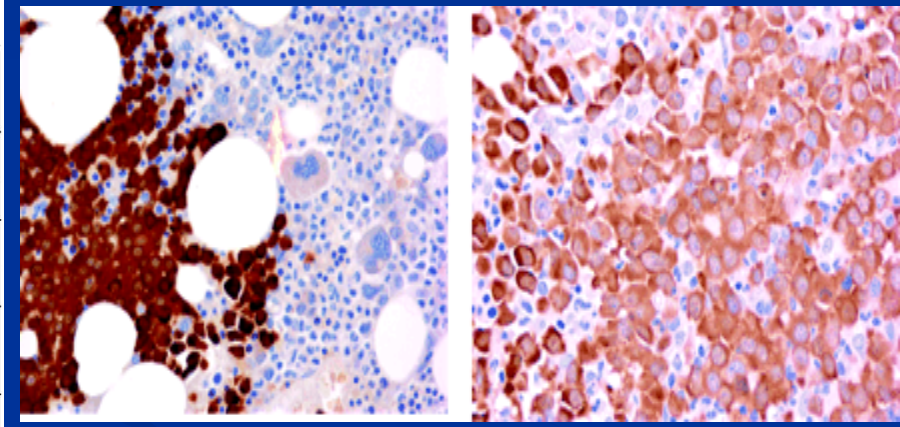


Vaccination with Individual Antigens

- Myeloma: MUC1, CYP1B1, PRAME, WT1, HSP96, Idiotype, Cancer Testis Antigens (NY-ESO)
- Advantages
  - Tumor specificity
  - Feasibility
  - Monitoring of immunologic response against defined antigen
- Disadvantages
  - Limited number of antigens
  - HLA restriction
  - Tumor evasion through down regulation of antigen expression

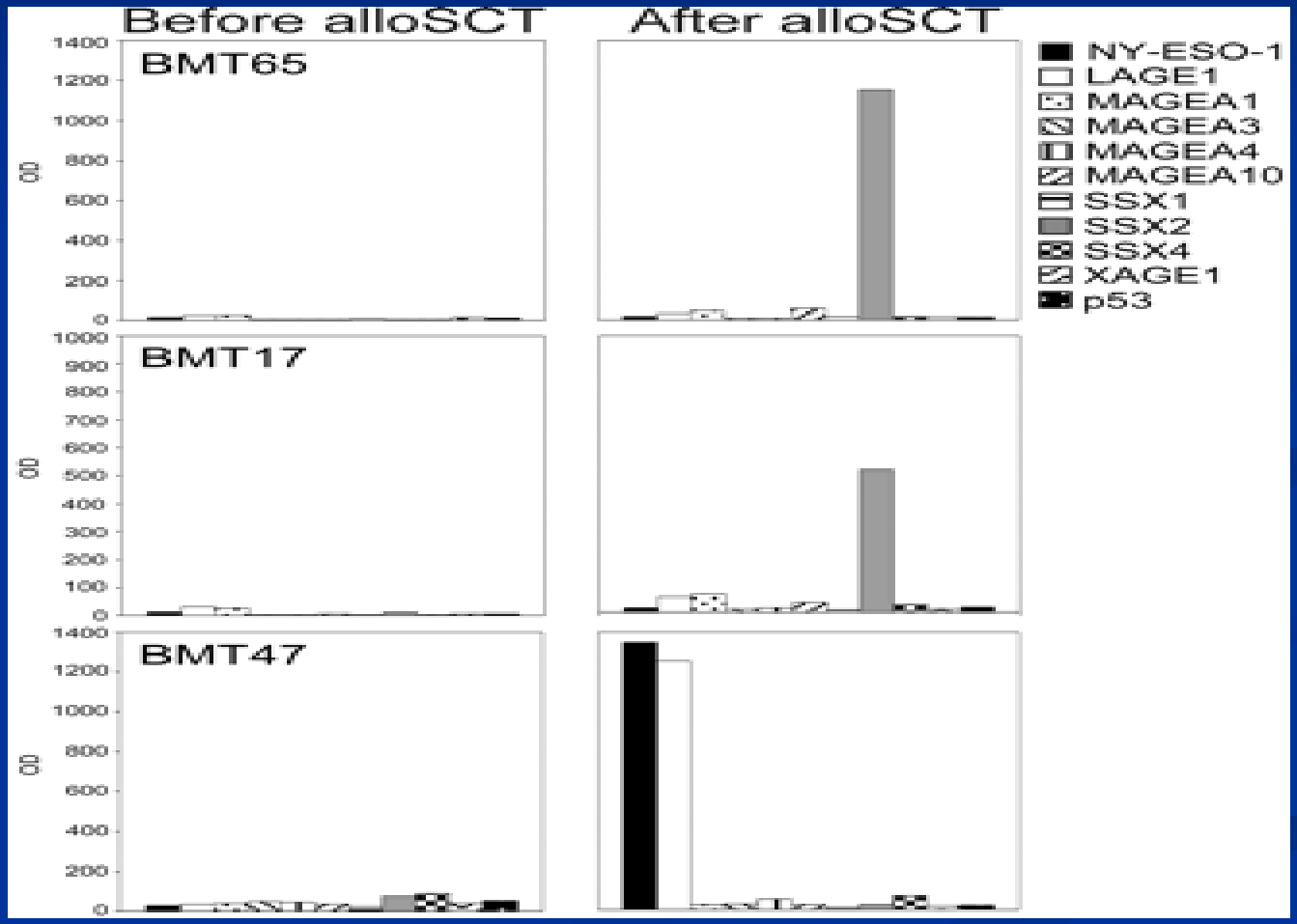
NY-ESO expression associated with advanced disease





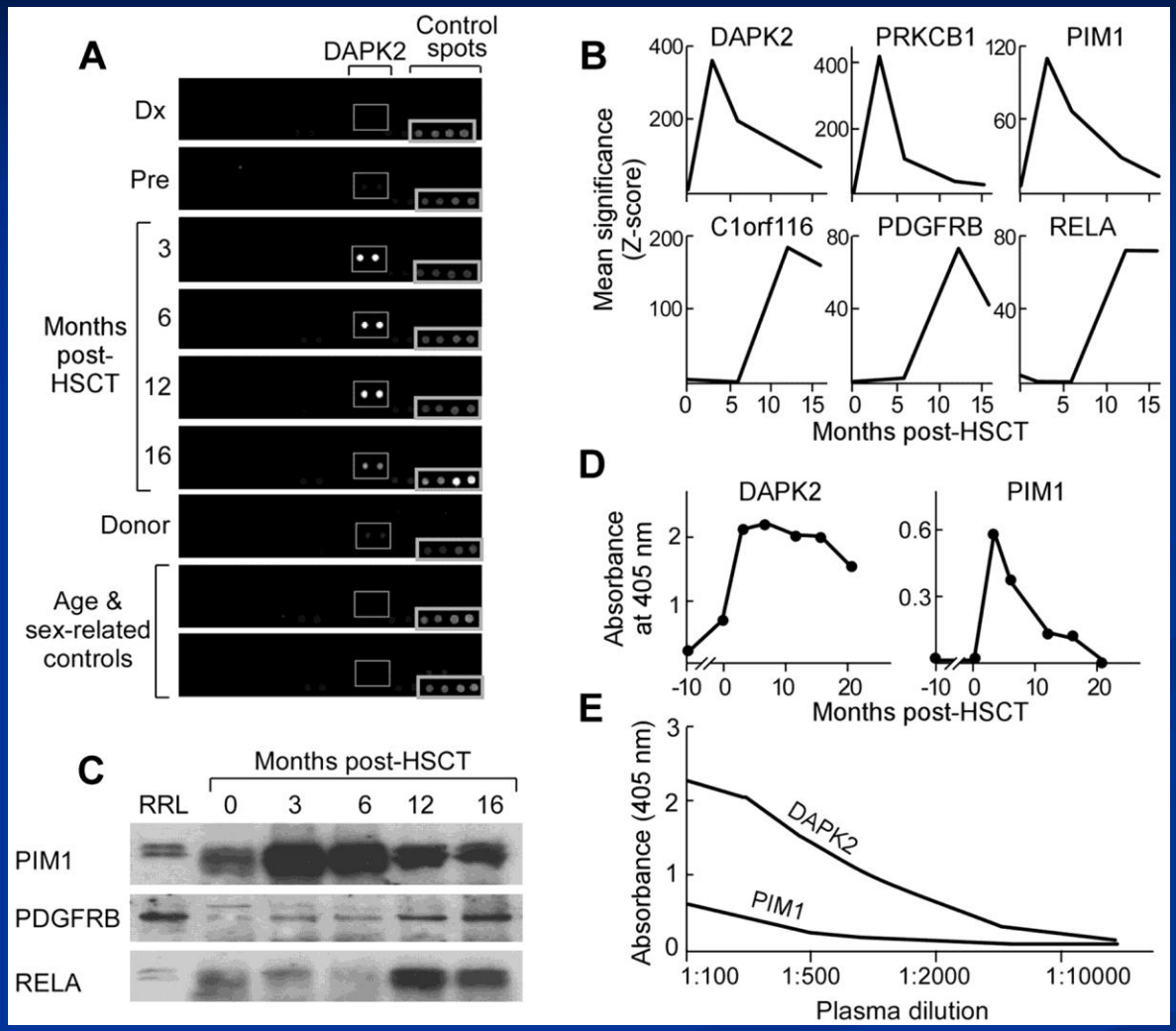
vanRhee, Frits, Blood, 2005

Humoral Response to Cancer Testis Antigens Post-allotransplant



Atanackovic, Djordje, Blood, 2007

Serologic screening identifies high-titer Ab responses against DAPK2, PDGFRB, PIM1, and PRKCB1 developing after syngeneic HSCT.



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Biernacki M A et al. Blood 2012;119:3142-3150

D1- and P4-specific CD8 T cells recognize primary MM tissue from HLA-A2–positive patients.

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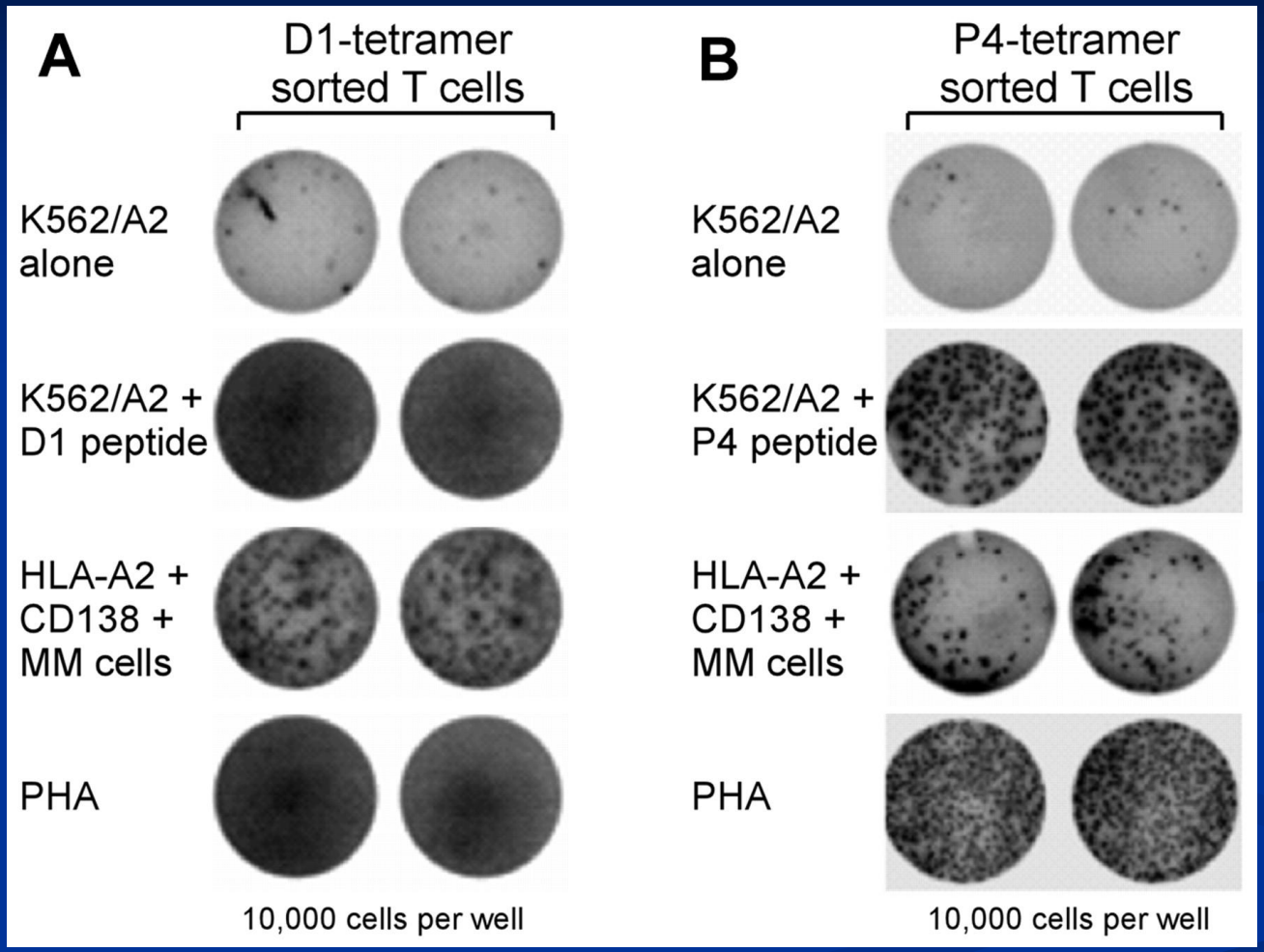
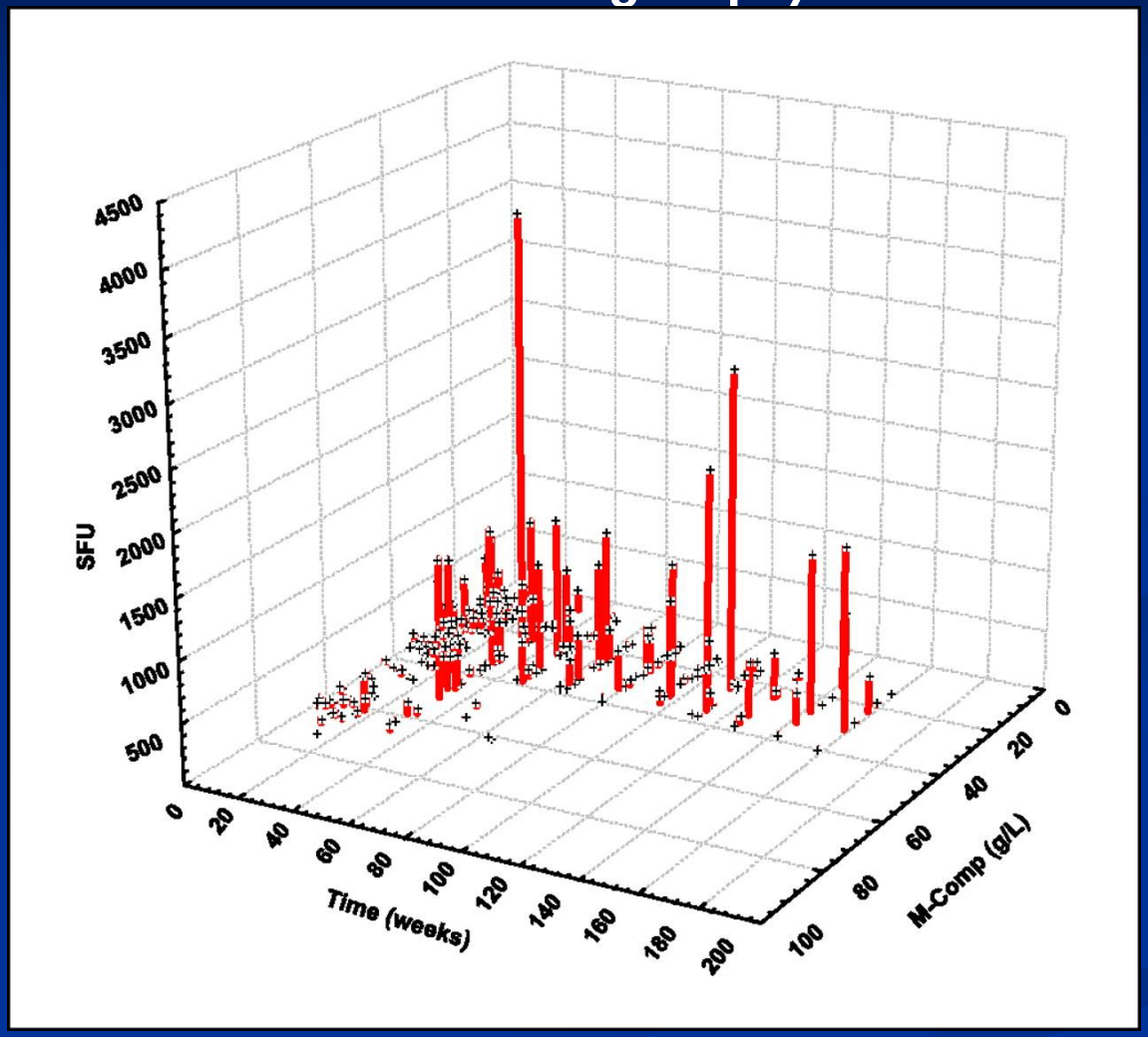


Biernacki M A et al. Blood 2012;119:3142-3150

Time kinetics of idiotype-induced IFN-γ–secreting T cells (ELISPOT) in relation to M-component concentration in all patients (both vaccination groups).

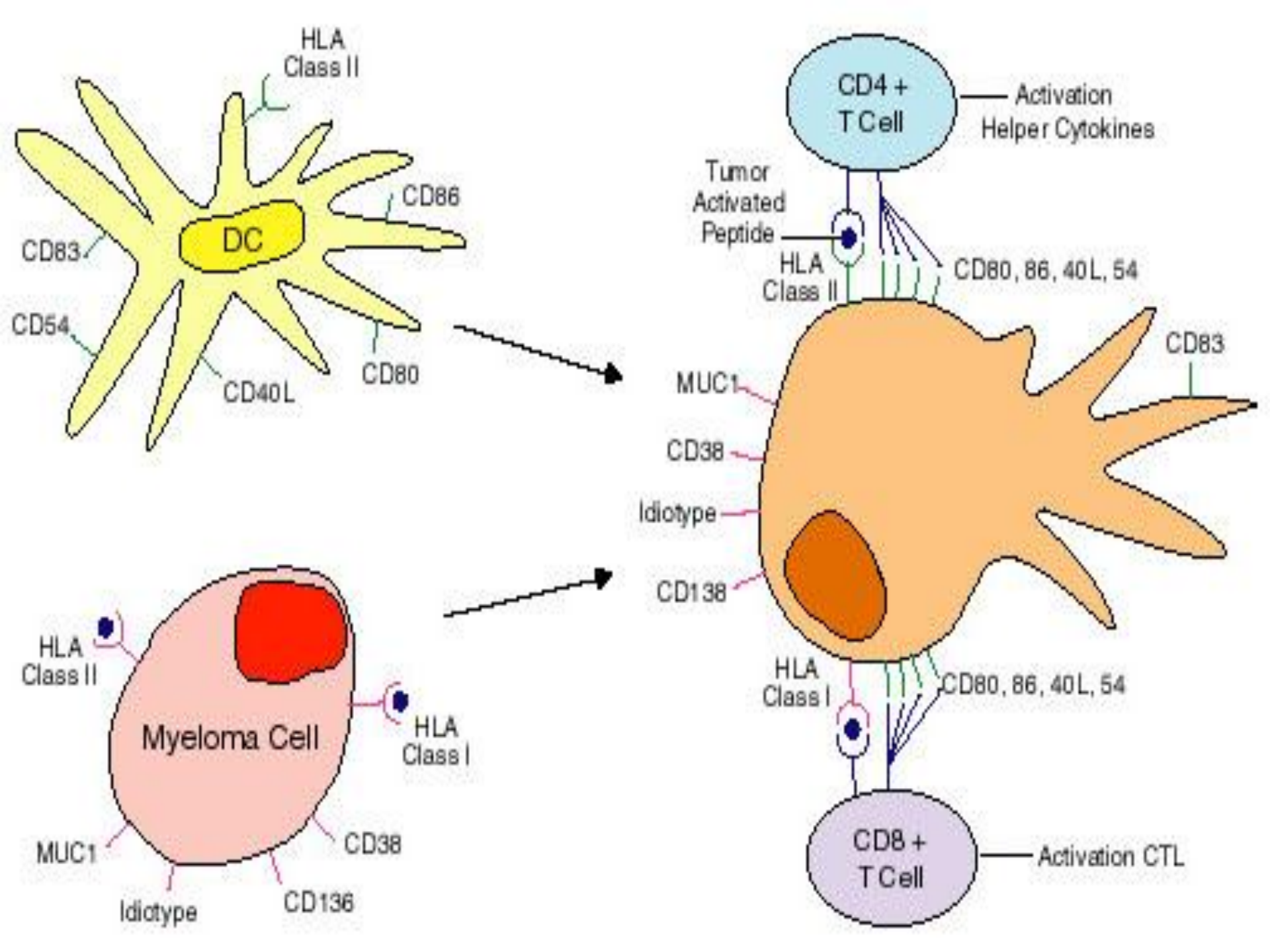


Hansson L et al. Clin Cancer Res 2007;13:1503-1510

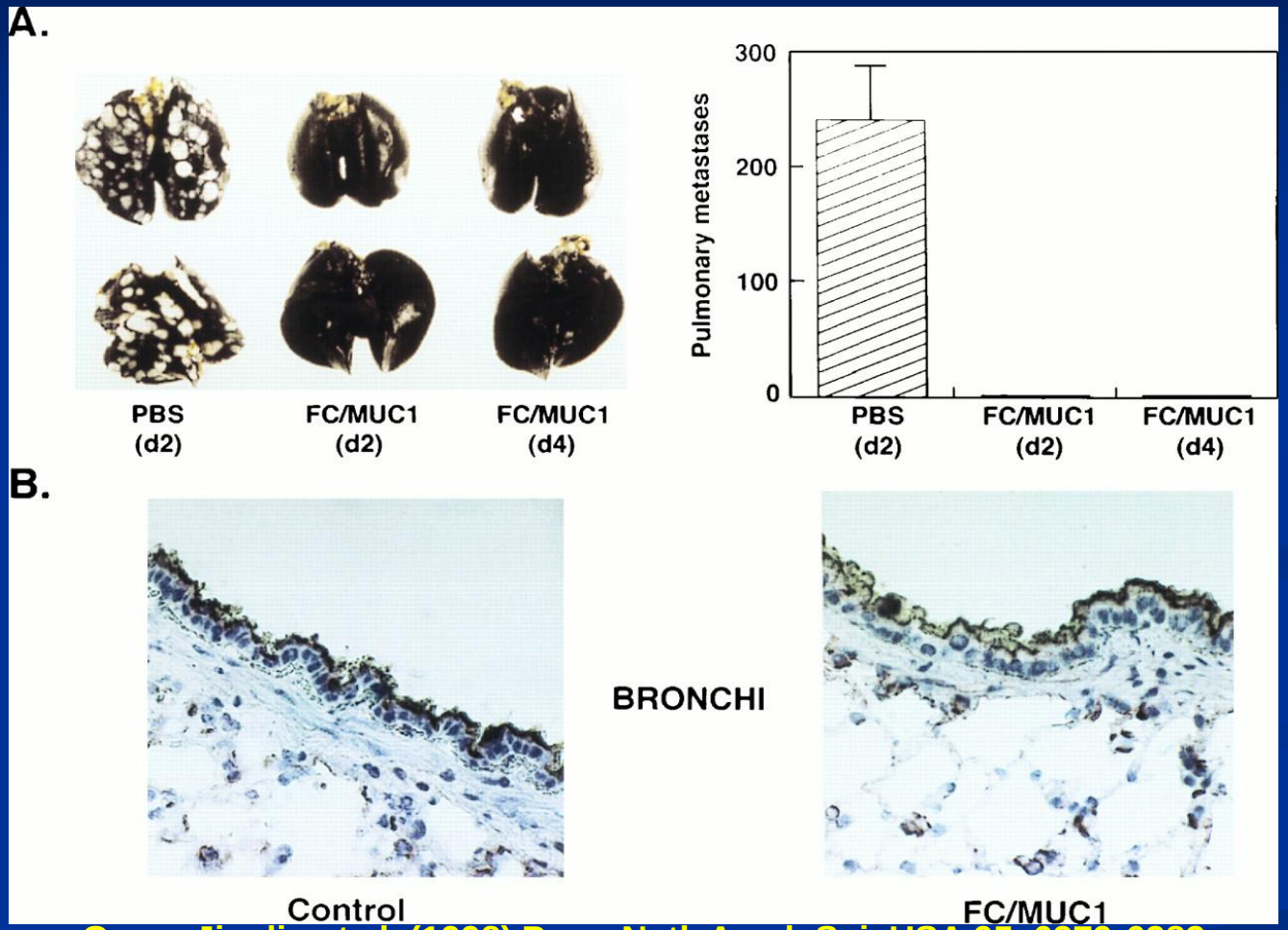
Clinical Cancer Research

Vaccination with Whole Cell Derived Antigens

- Advantages
  - Broad response limits risk of evasion
  - Presence of helper and CTL response crucial for the maintenance of long term immune response
  - Presentation of unidentified and patient specific antigens
- Disadvantages
  - Technical challenge of manipulating whole cells for multi-center setting
  - Risk of auto-immunity

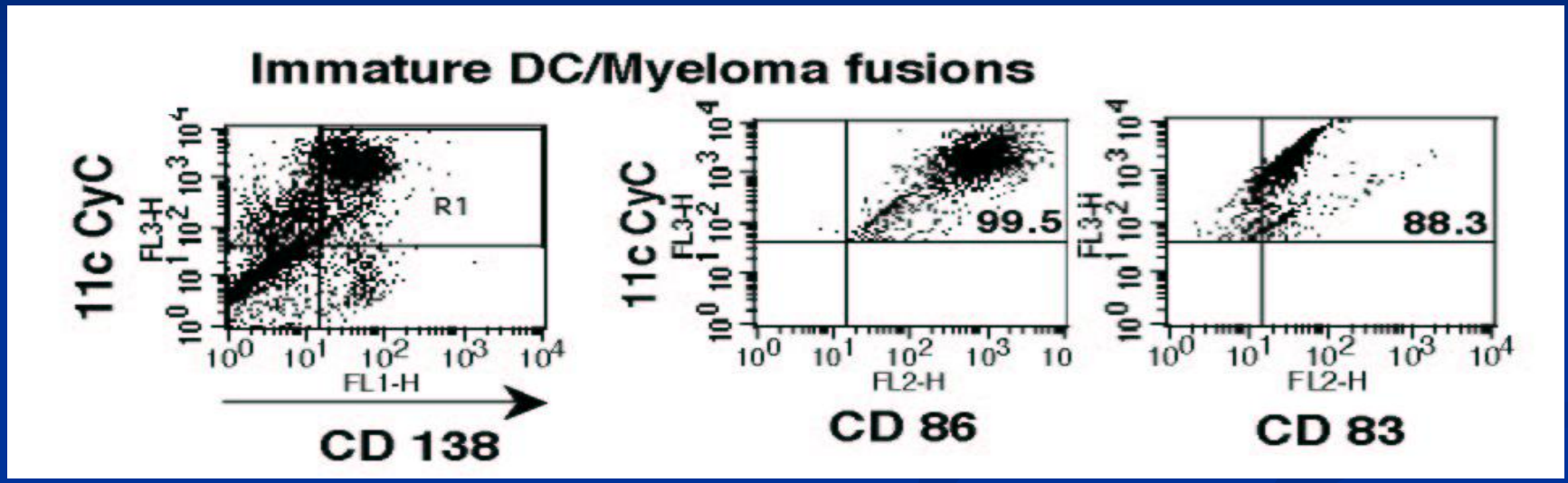

HLA
Class II
CD86
DC
CD83
CD54
CD40L
CD80
Myeloma Cell
HLA
Class II
HLA
Class I
MUC1
CD38
Idiotype
CD136
CD4 +
T Cell
Activation
Helper Cytokines
Tumor
Activated
Peptide
HLA
Class II
CD80, 86, 40L, 54
CD83
MUC1
CD38
Idiotype
CD138
HLA
Class I
CD80, 86, 40L, 54
CD8 +
T Cell
Activation CTL

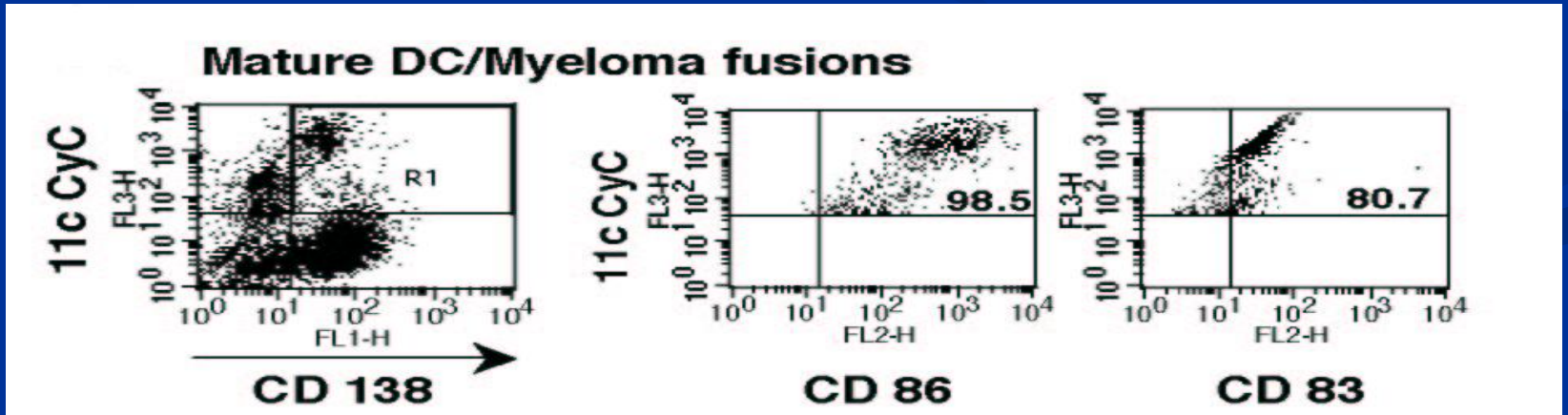
Animal Model: Fusion Vaccine Induces Disease Regression in Metastatic Disease



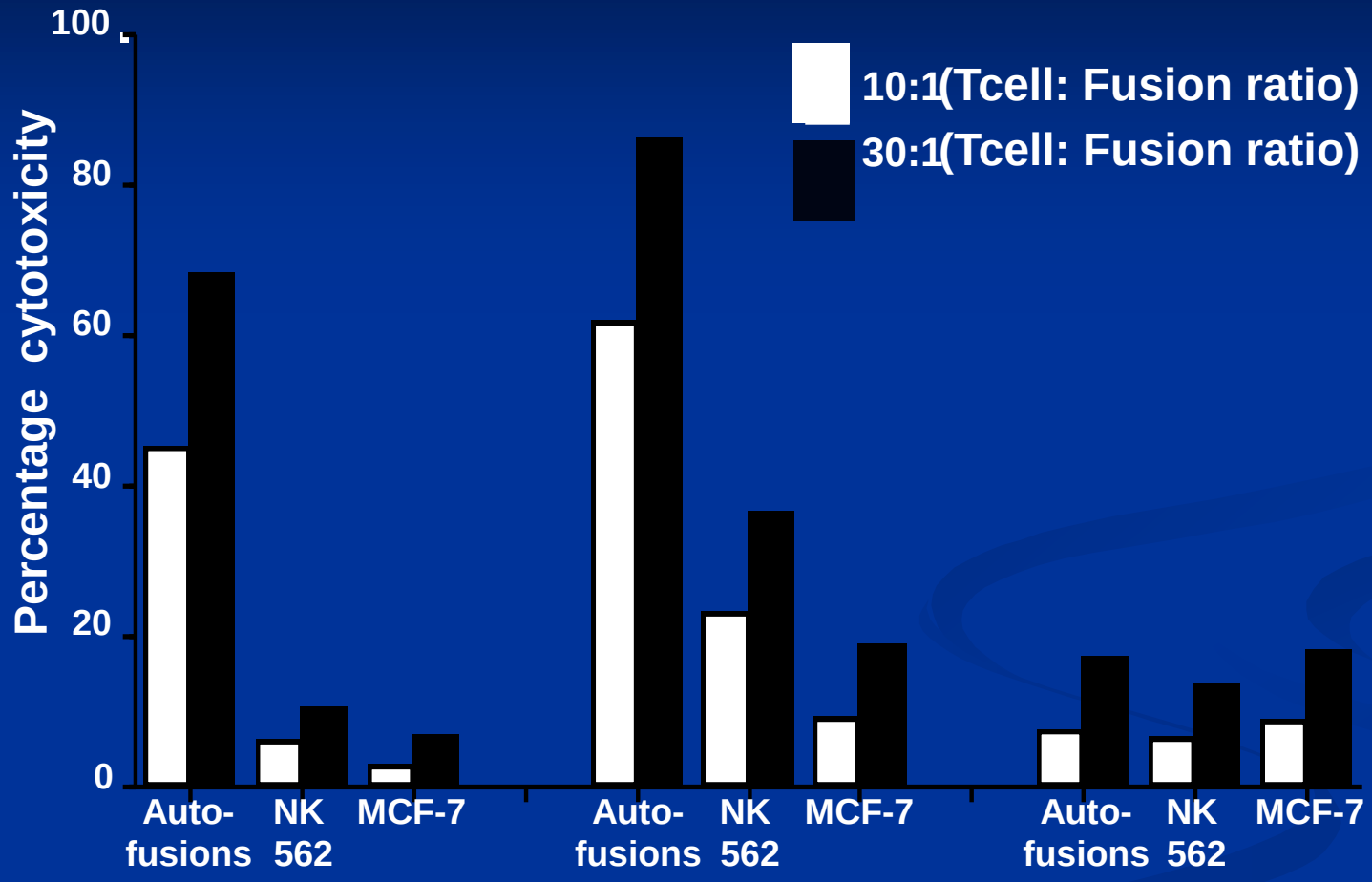
Gong, Jianlin et al. (1998) Proc. Natl. Acad. Sci. USA 95, 6279-6283

Biology of DC/MM Fusions

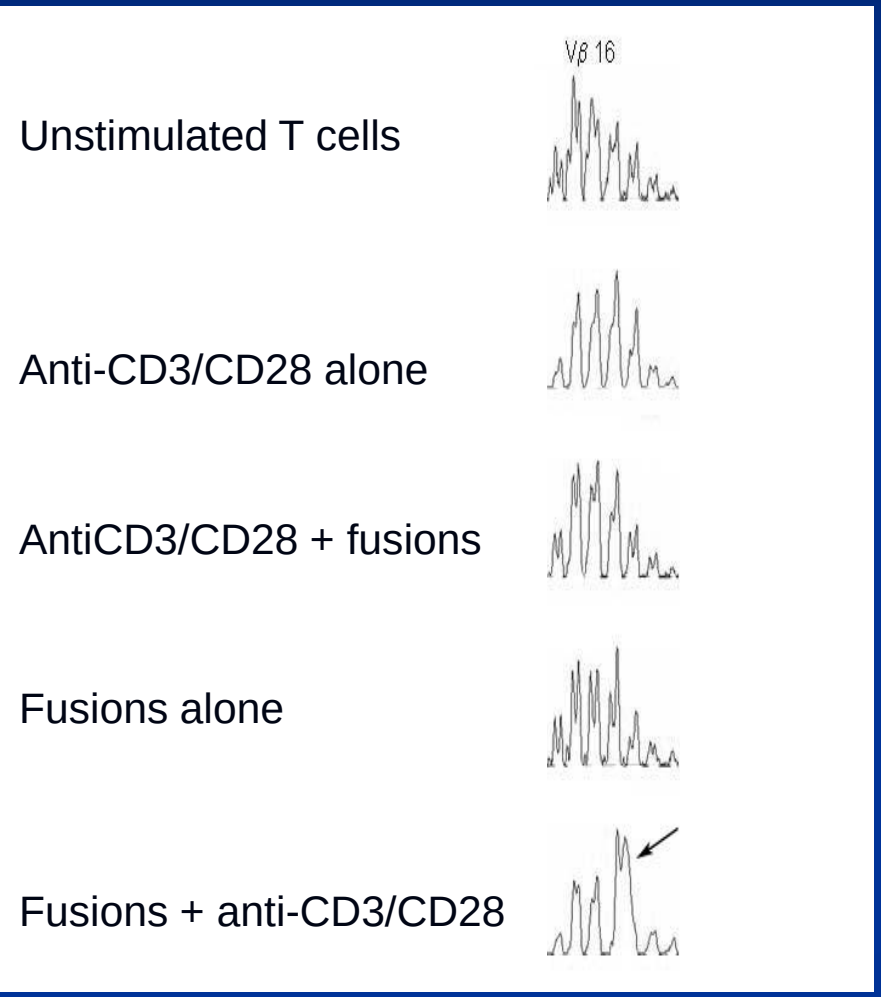


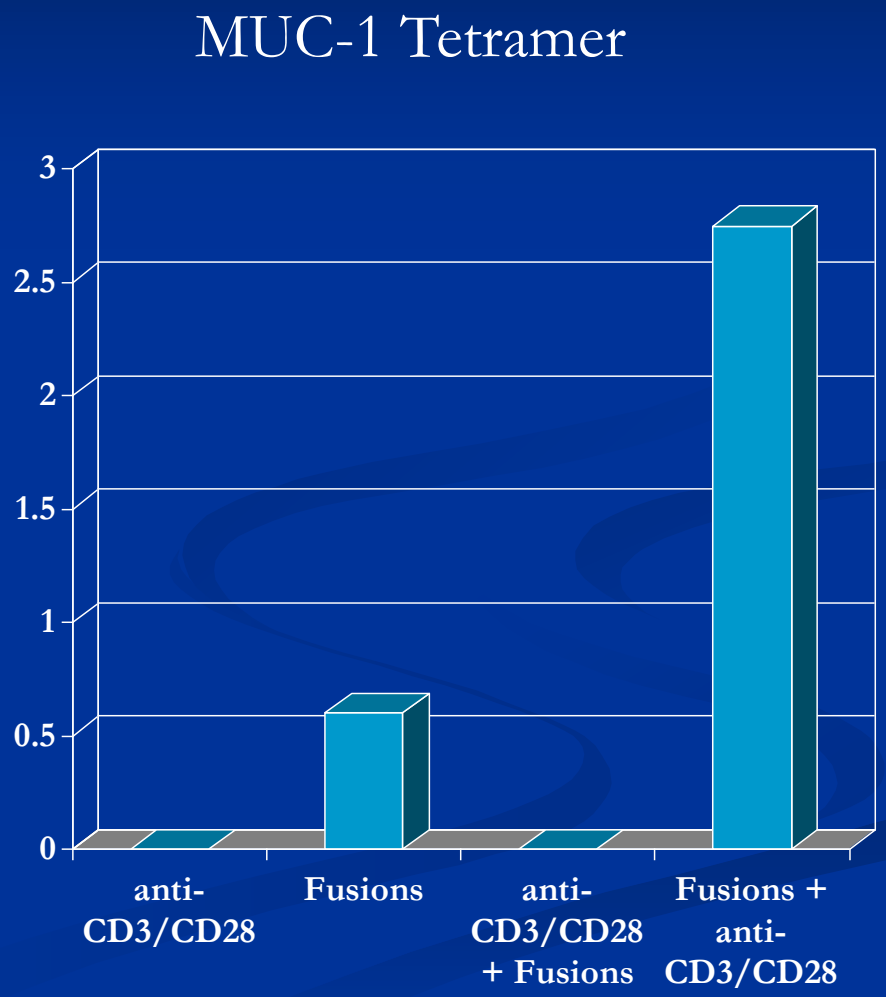


CTL Induced by Mature and Immature Fusions



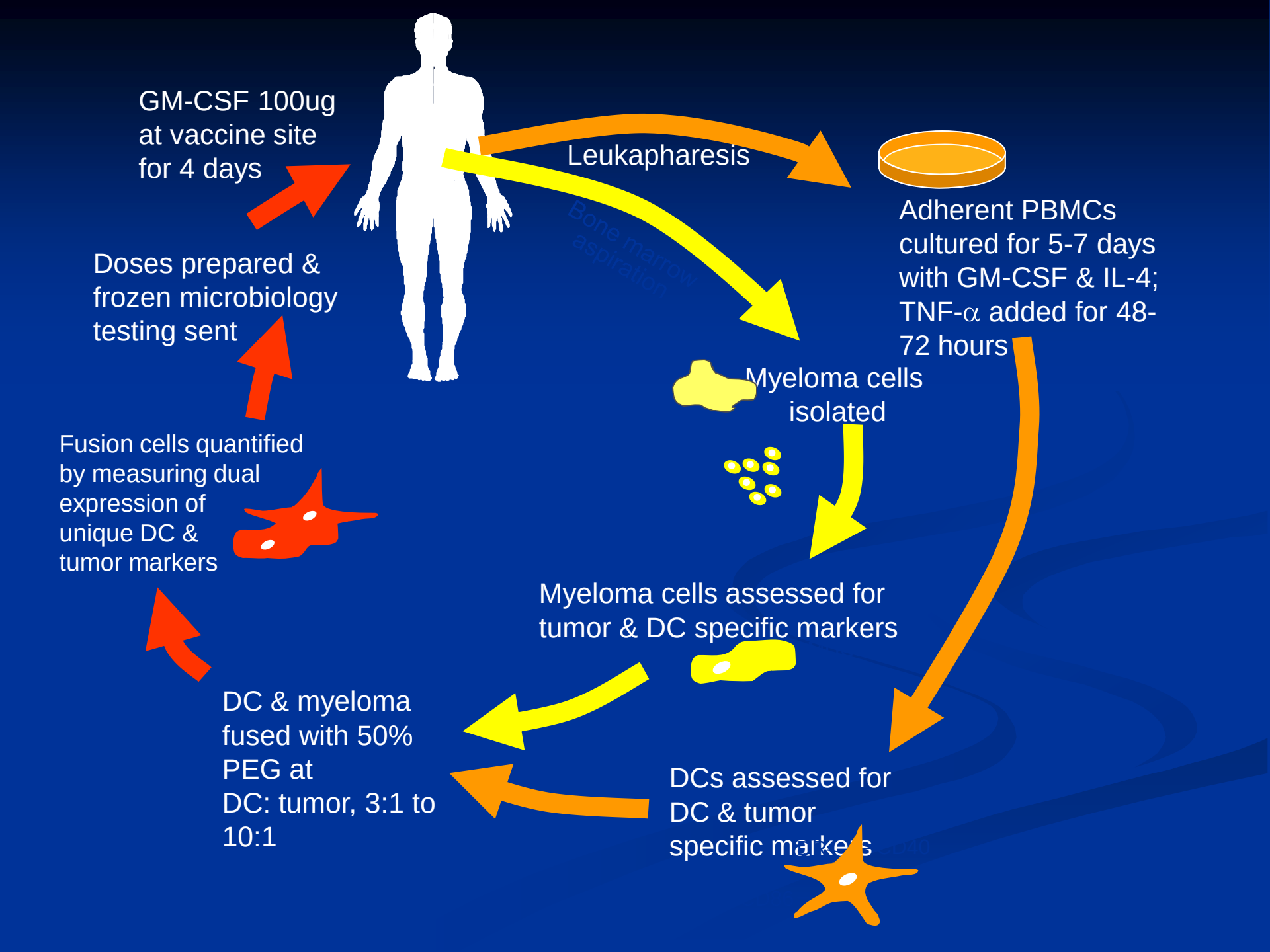
Expansion of Tumor Reactive T cells





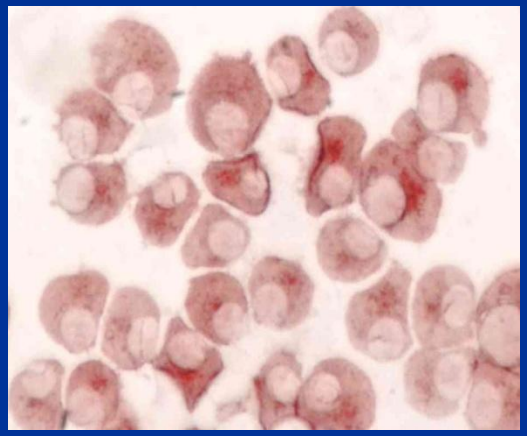
Vaccination with DC/MM Fusions: Trial Design

- Phase I dose escalation trial
- 17 patients have completed vaccination
- Mean age 57 years old
- Mean BM Plasma Cell Involvement: 35%
- Median number of prior treatment regimens: 4
- 14 patients with prior autologous transplant
- Vaccine Dose:
  - 3 patients: $1x10^6$
  - 4 patients: $2x10^6$
  - 9 patients: $4x10^6$

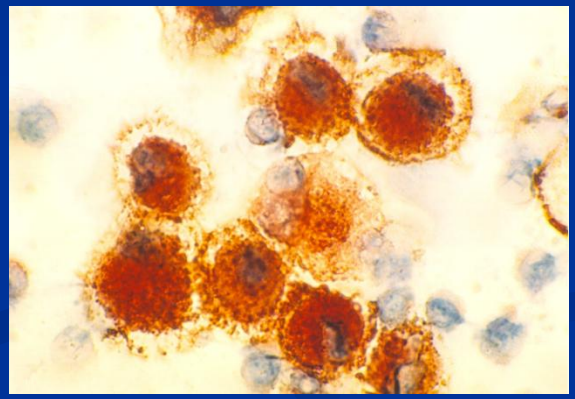

GM-CSF 100ug at vaccine site for 4 days
Leukapharesis
Adherent PBMCs cultured for 5-7 days with GM-CSF & IL-4; TNF-α added for 48-72 hours
Bone marrow aspiration
Myeloma cells isolated
Doses prepared & frozen microbiology testing sent
Fusion cells quantified by measuring dual expression of unique DC & tumor markers
Myeloma cells assessed for tumor & DC specific markers
DC & myeloma fused with 50% PEG at DC: tumor, 3:1 to 10:1
DCs assessed for DC & tumor specific markers

Vaccine Characterization

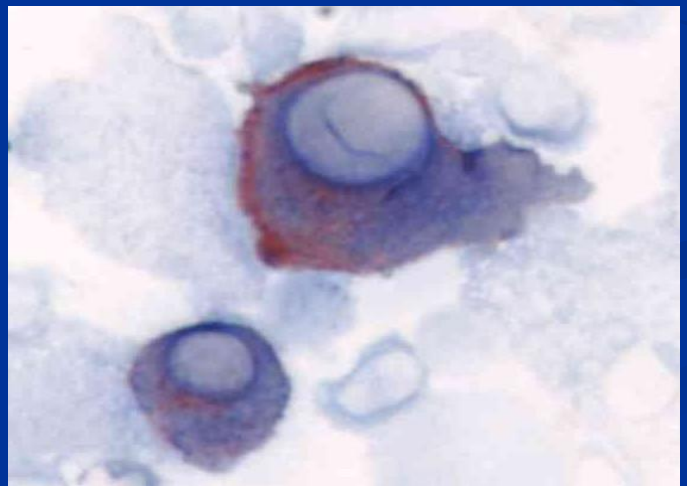
Myeloma Cells CD-38



Dendritic Cells CD86



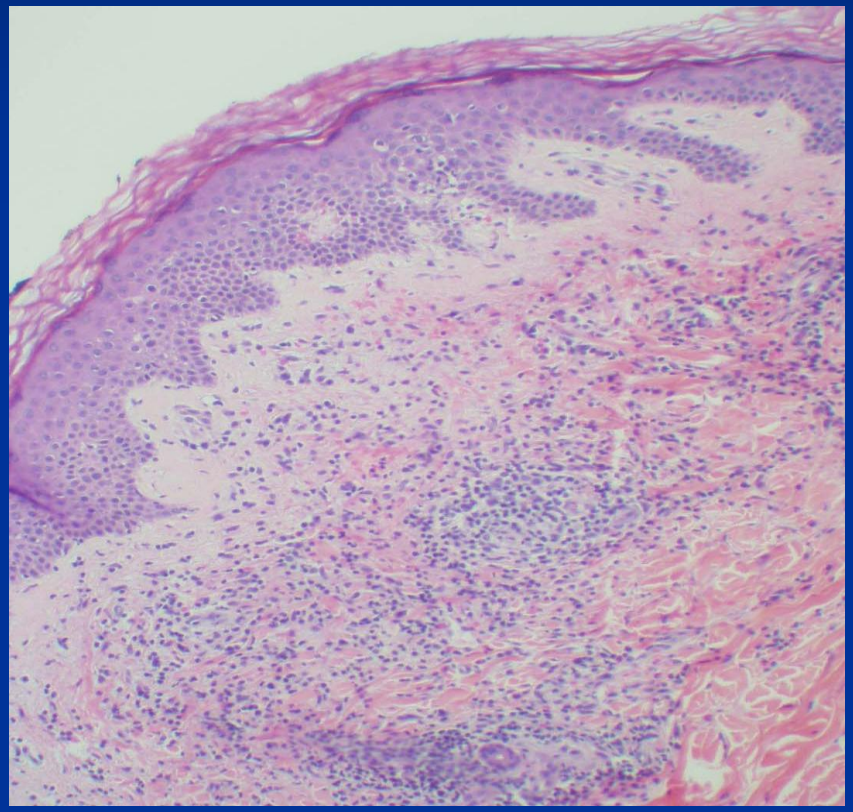
DC/MM Fusions
CD38/CD86



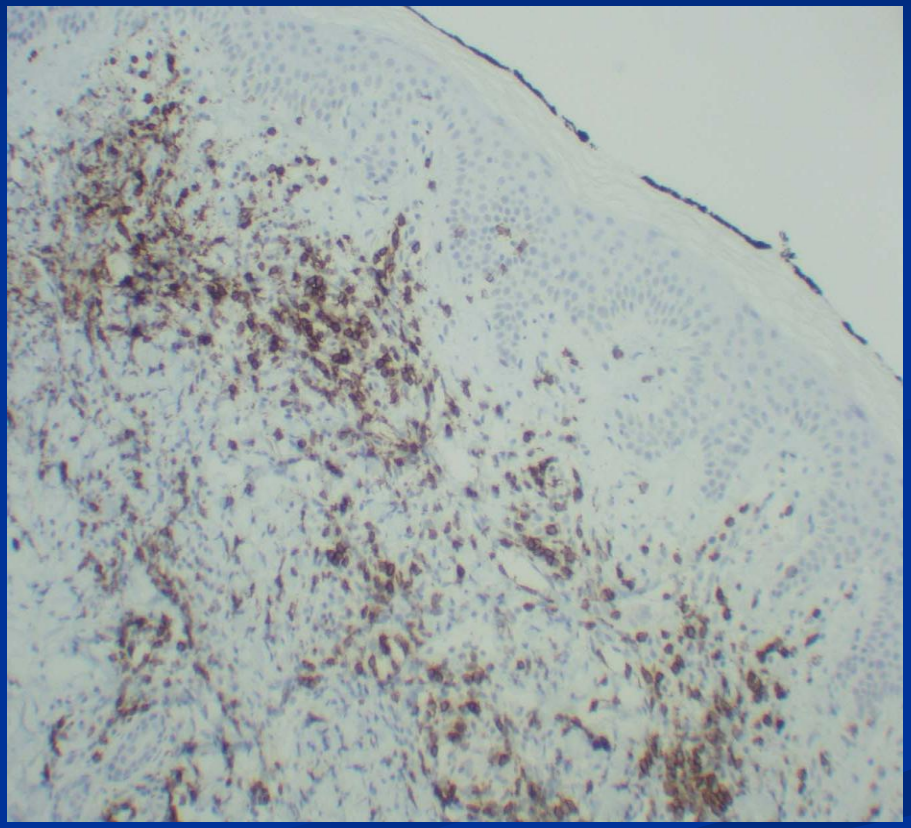
Adverse Events

- Treatment associated events transient grade I-II
  - Injection site reactions 37
  - Edema 6
  - Muscle Aches 5
  - Fatigue 2
  - Fever 1
  - Chills/sweats 2
  - Diarrhea 1
  - Pruritis 1
  - Rash 2
  - Anorexia 1
- Episode of DVT/PE with antecedent history of DVT

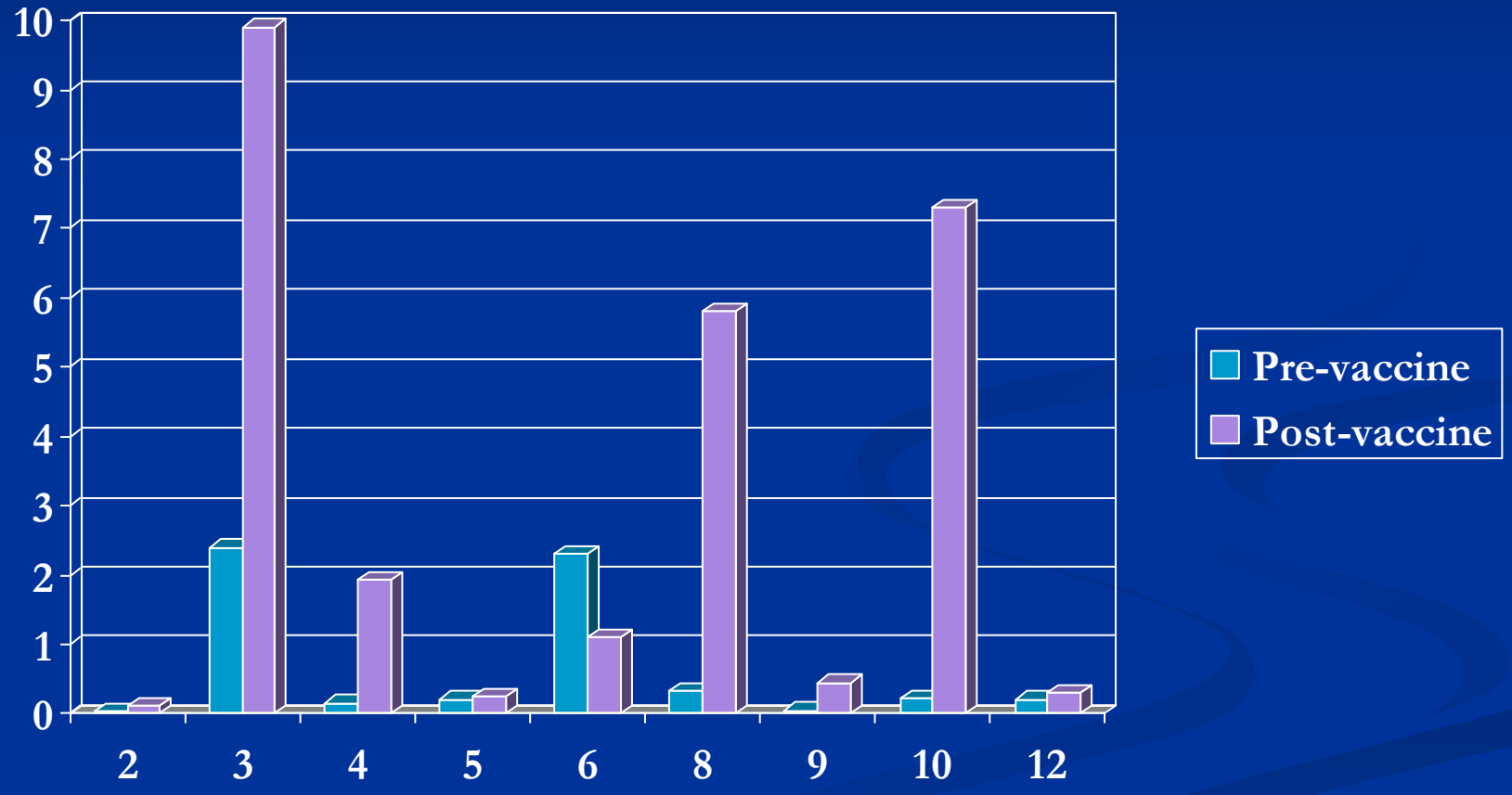
Vaccine site reaction: Skin Biopsy



CD8 Staining

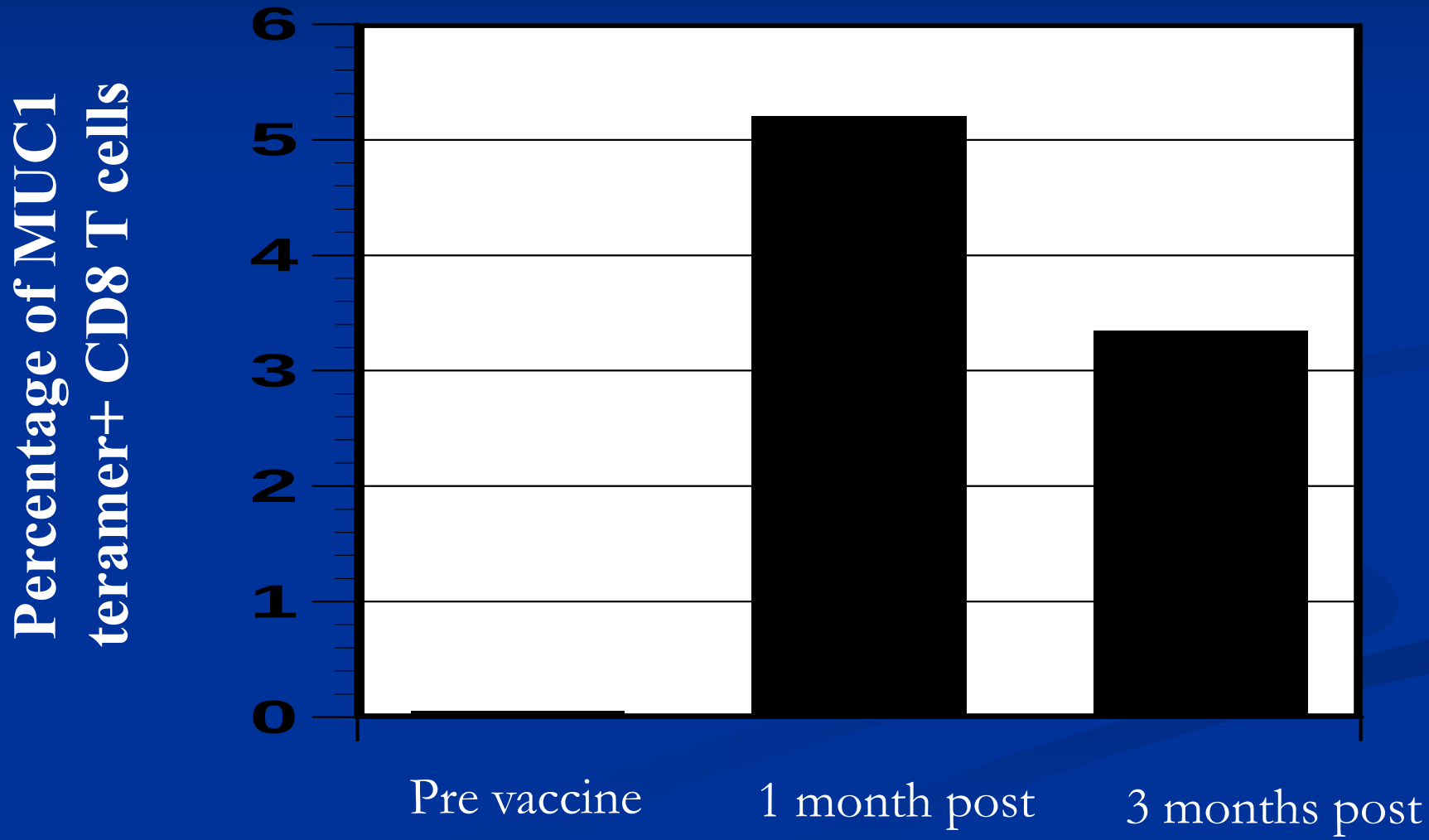


Tumor Lysate Induced IFNγ Expression by CD8+ T cells

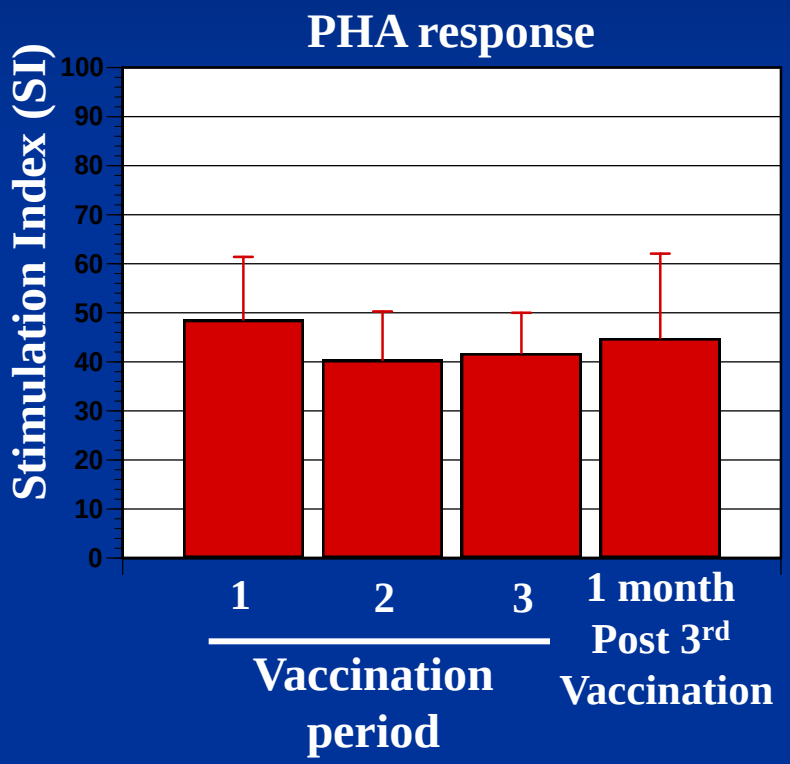


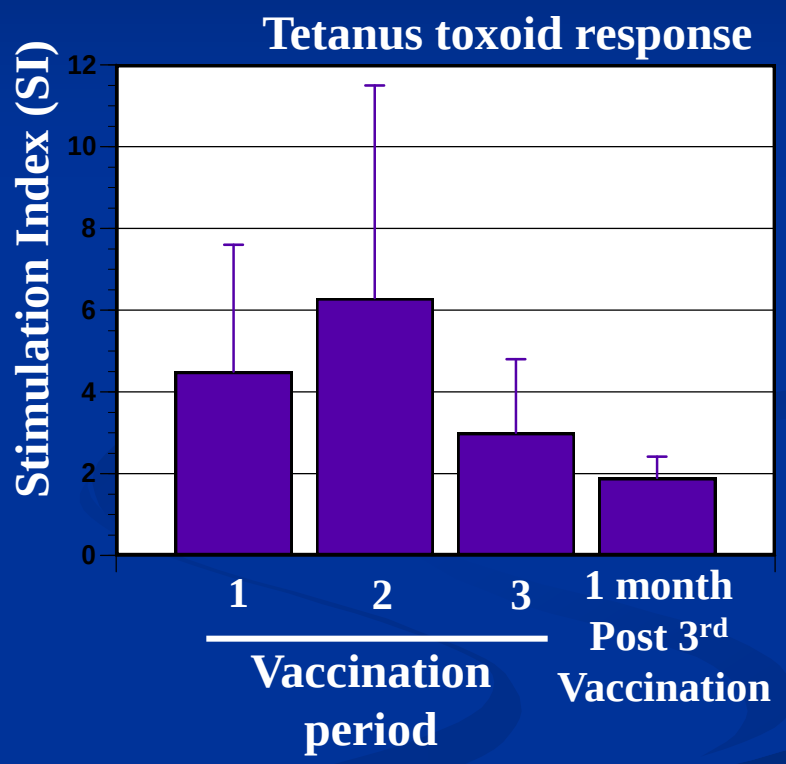
Mean fold increase = 9.5

Vaccine Induced Expansion of MUC1 Reactive T cells



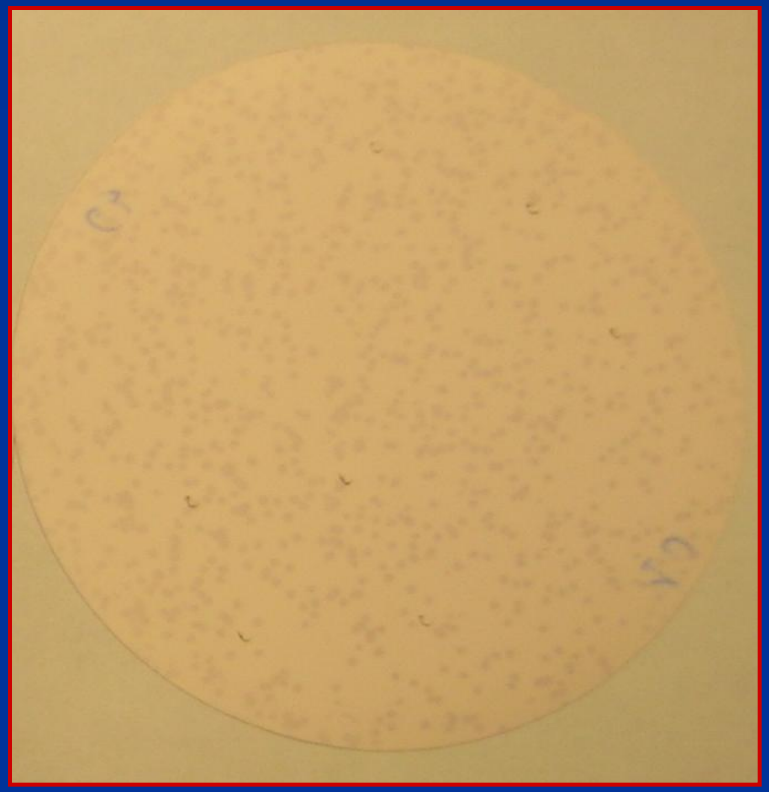
T cell Response to PHA and Tetanus Toxoid



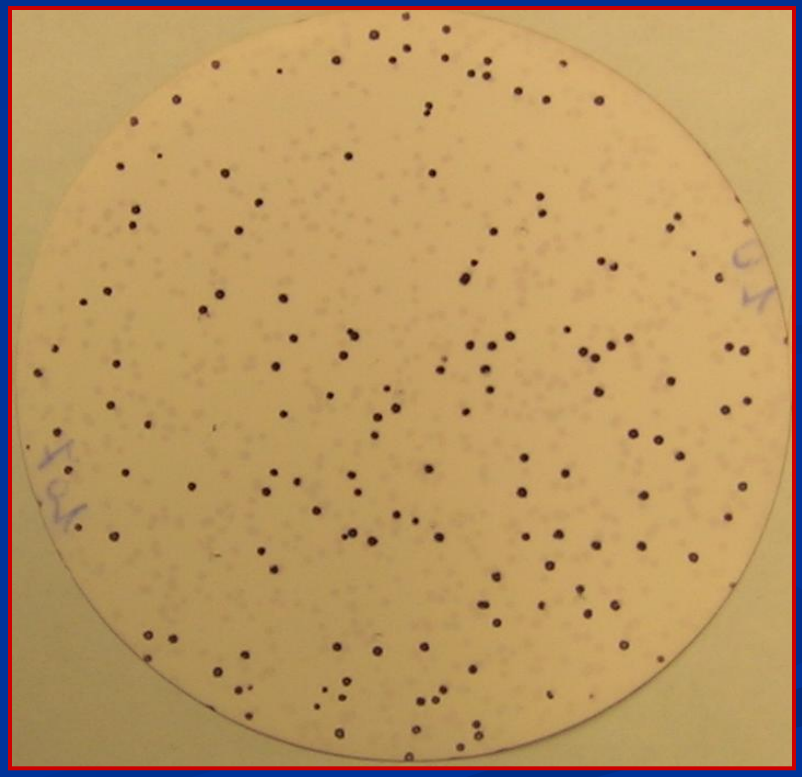


SEREX analysis of Humoral Response

Pre-vaccine serum from MM010 (RGS19 negative)



1 month post-vaccine serum from MM010 (RGS19 positive)



Vaccination with DC/Myeloma Fusions: Summary

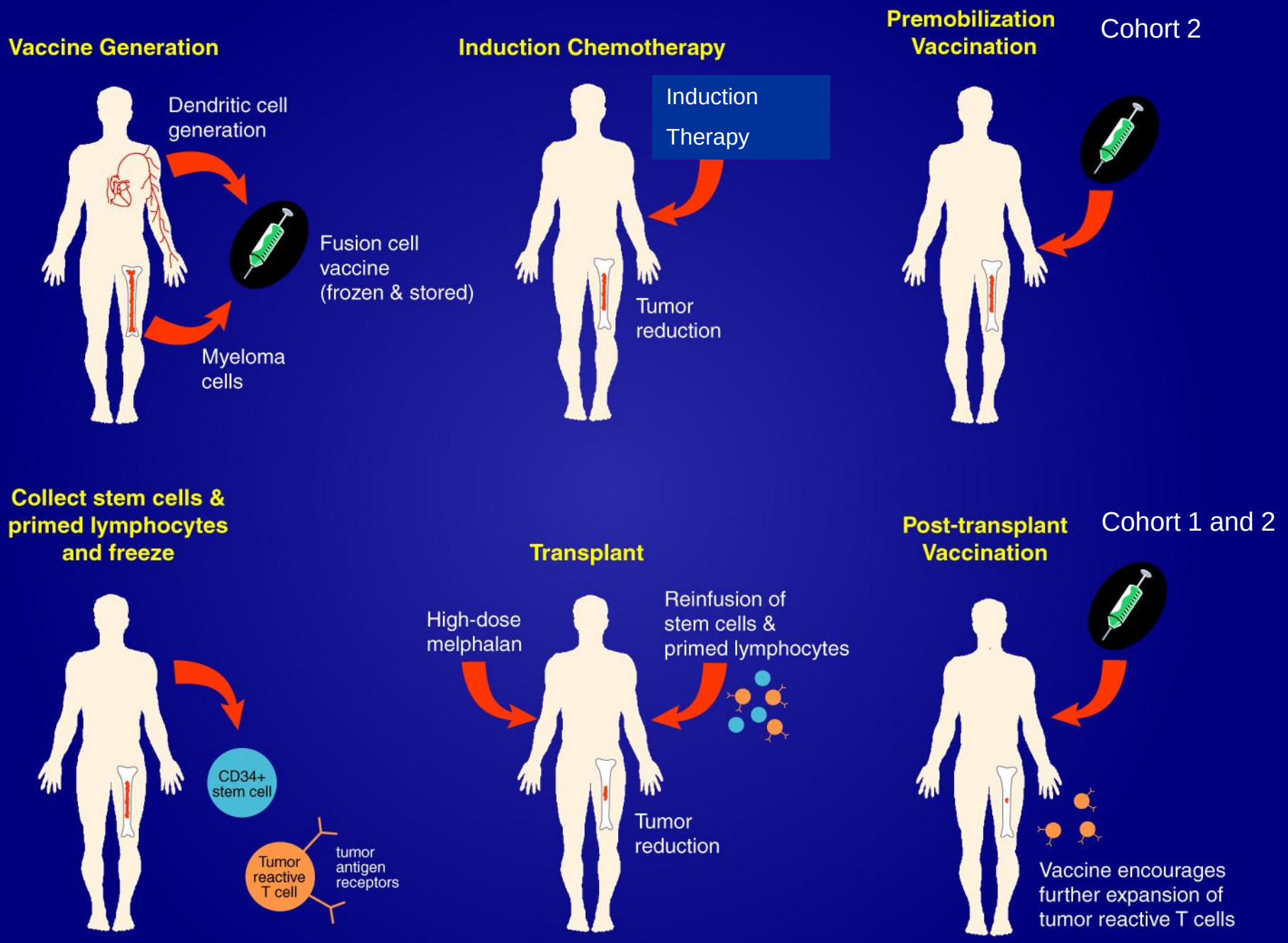
- 66% with disease stabilization for at least 2 months post-vaccination, 3 patients ongoing at 7, 14, and 30 m
- Vaccination is feasible and well tolerated
- A majority of patients with evidence of immunologic response
- Humoral response detected against novel antigens
- ? Of immunologic escape in some patients

Designing an Effective Cancer Vaccine

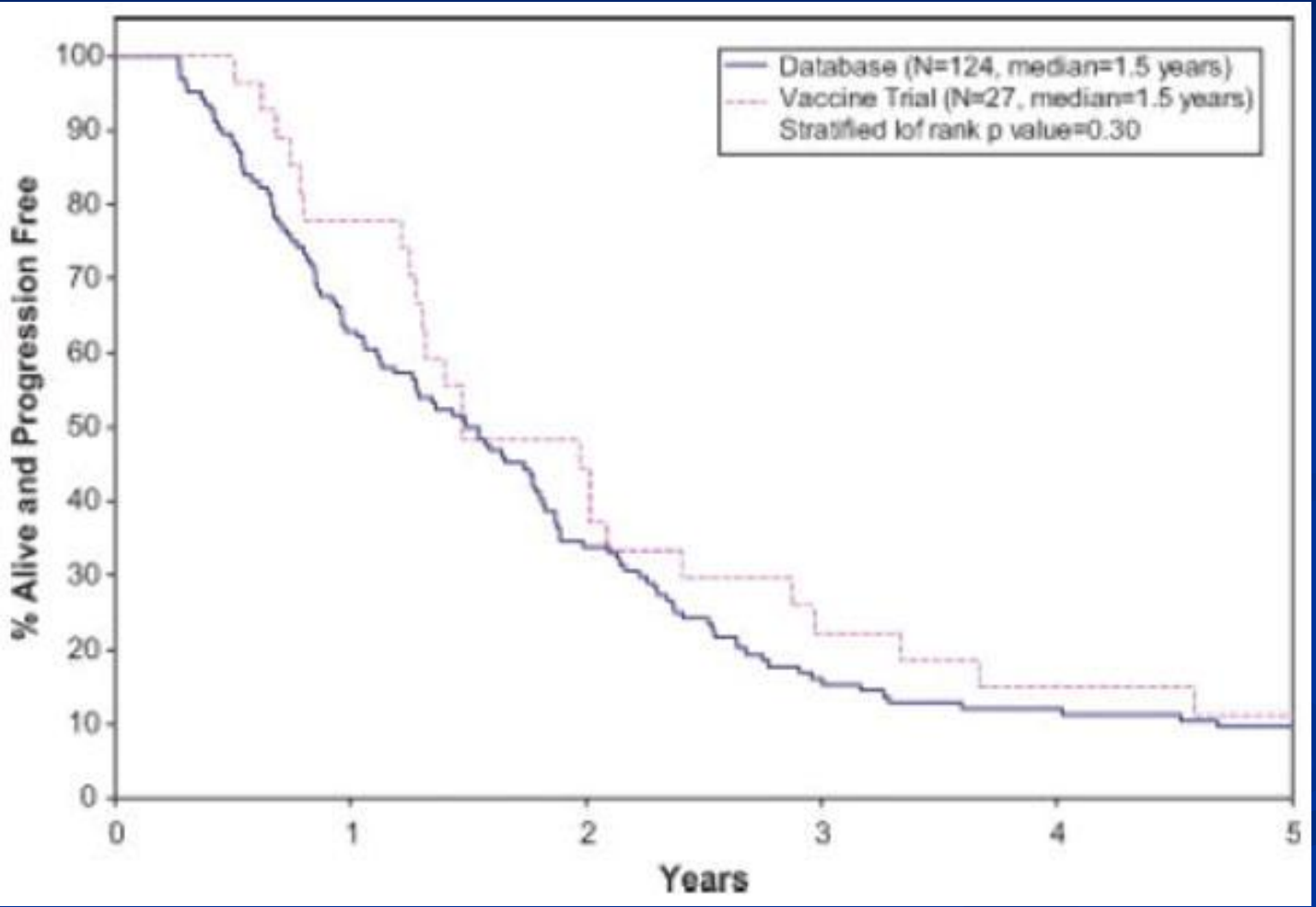
- Enhancing antigen presentation
  - Defining optimal antigenic targets
  - Effective antigen presentation to result in activation rather than tolerance
- Reversing the immunosuppressive milieu
  - Reversing effector cell dysfunction
  - Reduction in inhibitory cells
- Breaking tolerance establishing durable anti-tumor immunity
  - Downregulation of inhibitory pathways
- Targeting tumor heterogeneity

Vaccination in Conjunction with Stem Cell Transplant

- Autologous transplant for myeloma offers a unique opportunity to explore the role of cancer vaccines
  - Patients achieve minimal disease state but reliably relapse
  - Transplant mediated cytoreduction minimizes immunosuppression
- Enhanced response to vaccination post-transplant in animal models
  - Depletion of regulatory T cells during the period of post-transplant lymphopoietic reconstitution
  - Expansion of tumor reactive clones
- Will chemotherapy induced immune compromise prevent early response to vaccination?


Vaccine Generation
Dendritic cell generation
Fusion cell vaccine (frozen & stored)
Myeloma cells
Induction Chemotherapy
Induction Therapy
Tumor reduction
Premobilization Vaccination
Cohort 2
Collect stem cells & primed lymphocytes and freeze
CD34+ stem cell
Tumor reactive T cell
tumor antigen receptors
Transplant
High-dose melphalan
Reinfusion of stem cells & primed lymphocytes
Tumor reduction
Post-transplant Vaccination
Cohort 1 and 2
Vaccine encourages further expansion of tumor reactive T cells

Idiotype based vaccine post-transplant
No difference in progression free survival



Lacy AM J Hematol 2009; 84(12)P799-802

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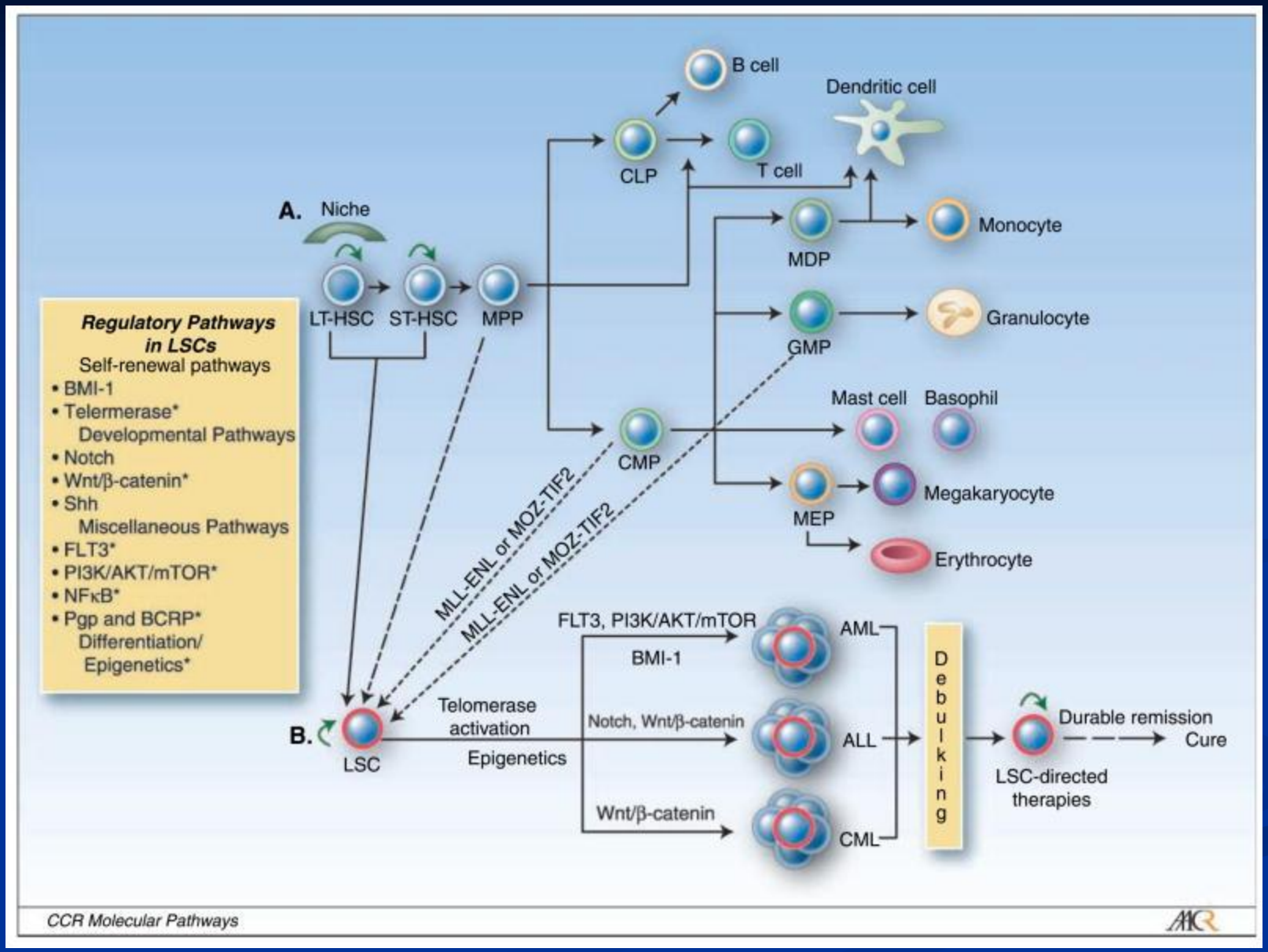
- Breaking tolerance establishing durable anti-tumor immunity
  - Downregulation of inhibitory pathways
- Targeting tumor heterogeneity
  - Targeting the malignant stem cell
  - Stromal cells


B cell
Dendritic cell
CLP
T cell
A. Niche
Monocyte
MDP
LT-HSC
ST-HSC
MPP
Granulocyte
GMP
Regulatory Pathways in LSCs
Self-renewal pathways
• BMI-1
• Telermerase*
Developmental Pathways
• Notch
• Wnt/β-catenin*
• Shh
Miscellaneous Pathways
• FLT3*
• PI3K/AKT/mTOR*
• NFκB*
• Pgp and BCRP*
Differentiation/ Epigenetics*
Mast cell
Basophil
CMP
Megakaryocyte
MEP
Erythrocyte
MLL-ENL or MOZ-TIF2
MLL-ENL or MOZ-TIF2
FLT3, PI3K/AKT/mTOR
AML
BMI-1
Telomerase activation
Epigenetics
Notch, Wnt/β-catenin
ALL
Debulking
Durable remission
Cure
B.
LSC
LSC-directed therapies
Wnt/β-catenin
CML
CCR Molecular Pathways

Vaccine Therapy: Questions Remain

- Whole cell vs. individual antigen
  - Multiple antigenic targets potentially augments efficacy via polyclonal response and targeting heterogeneity but ? feasibility
- Ex vivo vs. endogenous DCs
  - Feasibility of Cell Manipulation
- Preventing reestablishment of tolerance
- Setting dictates design
  - Low disease volume likely most suited but requires large randomized trial design before we know what is the best approach